DISSERTATION ON

COMPARATIVE STUDY OF EFFICACY OF AUTOLOGOUS SERUM OPHTHALMIC SOLUTION VERSUS TEAR SUBSTITUTE AS ADJUVANT THERAPY IN THE TREATMENT OF OCULAR SURFACE DISORDERS

Submitted in partial fulfillment of requirements of

M.S.OPHTHALMOLOGY

BRANCH – III

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CERTIFICATE

This is to certify that the dissertation titled "**COMPARATIVE STUDY OF EFFICACY OF AUTOLOGOUS SERUM OPHTHALMIC SOLUTION VERSUS TEAR SUBSTITUTE AS ADJUVANT THERAPY IN THE TREATMENT OF OCULAR SURFACE DISORDERS**" is a bonafide record of the research work done by **DR. VANITHA.R,** Post graduate in the Regional Institute of Ophthalmology & Government Ophthalmic Hospital, Madras Medical College and Government General Hospital, Chennai-03, in partial fulfillment of the regulations laid down by the Tamil Nadu Dr. M.G.R Medical University for the award of M.S. Ophthalmology Branch III, under my guidance and supervision during the academic year2014– 2017.

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PLACE:

ACKNOWLEDGEMENT

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The following members of Ethics Committee were present in the meeting hold on **07.06.2016** conducted at Madras Medical College, Chennai 3

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We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

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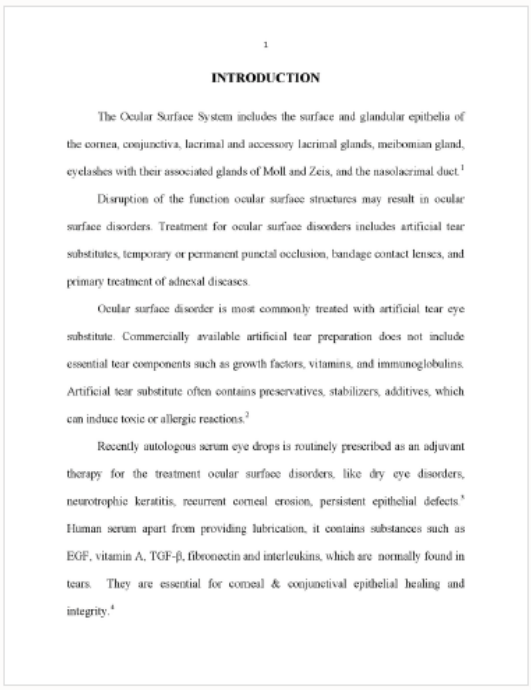

1

INTRODUCTION

The Ocular Surface System includes the surface and glandular epithelia of the cornea, conjunctiva, lacrimal and accessory lacrimal glands, meibomian gland, eyelashes with their associated glands of Moll and Zeis, and the nasolacrimal duct.[1]

Disruption of the function ocular surface structures may result in ocular surface disorders. Treatment for ocular surface disorders includes artificial tear substitutes, temporary or permanent punctal occlusion, bandage contact lenses, and primary treatment of adnexal diseases.

Ocular surface disorder is most commonly treated with artificial tear eye substitute. Commercially available artificial tear preparation does not include essential tear components such as growth factors, vitamins, and immunoglobulins. Artificial tear substitute often contains preservatives, stabilizers, additives, which can induce toxic or allergic reactions.[2]

Recently autologous serum eye drops is routinely prescribed as an adjuvant therapy for the treatment ocular surface disorders, like dry eye disorders, neurotrophic keratitis, recurrent corneal erosion, persistent epithelial defects.[3] Human serum apart from providing lubrication, it contains substances such as EGF, vitamin A, TGF-β, fibronectin and interleukins, which are normally found in tears. They are essential for corneal & conjunctival epithelial healing and integrity.[4]

AIMS AND OBJECTIVES

OBJECTIVE/AIM:

To compare the efficacy of autologous serum ophthalmic solution Vs tear drops as adjuvant therapy in the treatment of ocular surface diseases.

PRIMARY OBJECTIVE:

To compare the efficacy of autologous serum ophthalmic solution Vs tear drops as adjuvant therapy in the treatment of ocular surface diseases.

SECONDARY OBJECTIVE:

1. To document prevalence of ocular surface diseases.
2. To document the symptoms and clinical features of patients presented with ocular surface diseases

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PART I

INTRODUCTION

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Recently autologous serum eye drops is routinely prescribed as an adjuvant therapy for the treatment ocular surface disorders, like dry eye disorders, neurotrophic keratitis, recurrent corneal erosion, persistent epithelial defects.[3-5] Human serum apart from providing lubrication, it contains substances such as EGF, vitamin A, TGF-β, fibronectin and interleukins, which are normally found in tears. They are essential for corneal &conjunctival epithelial healing and integrity.[4]

APPLIED ANATOMY

THE OCULAR SURFACE SYSTEM

Maintenance and protection of the smooth refractive surface of the cornea is the function of the Ocular Surface System.

The Ocular Surface System contains

- Surface and glandular epithelia of the cornea and conjunctiva,
- Lacrimal gland and accessory lacrimal glands,
- Meibomian gland, and their apical (tears) and basal (connective tissue) matrices,
- Glands of Moll and Zeis,
- Nasolacrimal duct.[1]

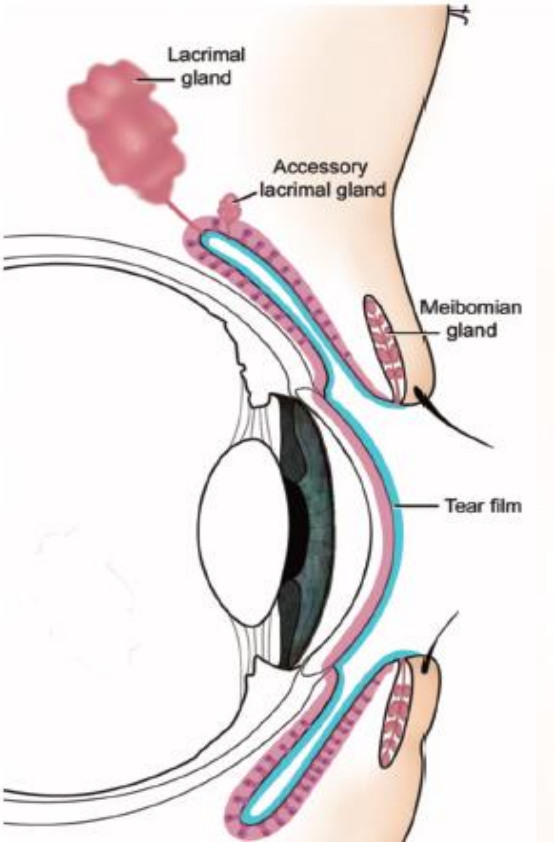
The Ocular Surface System encompasses different ocular structures. They are brought the name “Ocular Surface System” because

- All components are derived from the surface ectoderm
- They are linked by continuity of the epithelia,
- They are controlled by common innervations, and by the endocrine systems.

- They function synchronously to provide, protect and maintain a smooth refractive ocular surface[6].

Sagittal section through the ocular surface system is depicted below (Fig 1). It shows the continuity of the ocular surface epithelium (in pink) with regional specializations. Blue line depicts the pre ocular tear film.

Fig 1



LACRIMAL FUNCTION UNIT

It includes the ocular surface system along with the sensory and motor innervations which act together and not in isolation[7].

TEAR FILM

Tear film is a complex fluid mixture, essential for protecting, nourishing, and maintaining the health of the ocular surface.

The tear film contains the secretions of the

- lacrimal gland,
- accessory lacrimal glands of Krause and Wolfring,
- meibomian glands,
- glands of Zeis and Moll,
- conjunctival goblet cells, [8, 9].

The lacrimal system can be divided functionally into two parts:

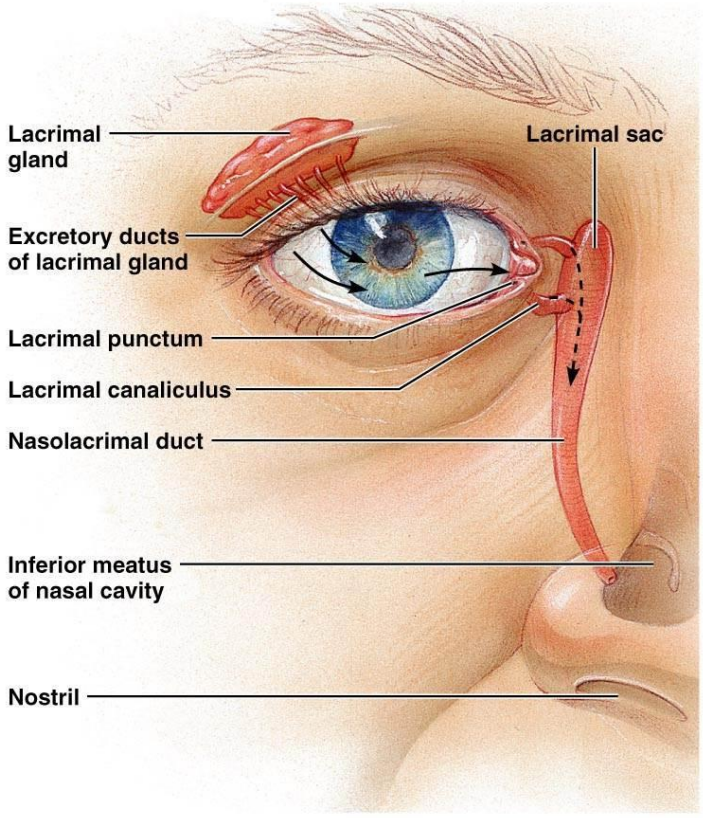
- **Basal secretors** (goblet cells, accessory lacrimal glands of Krause and Wolfring, , and meibomian, Zeis& Moll glands)
- **Reflex secretors** (the lacrimal gland) [10].

Glands contributing to the tear film are described briefly below.

LACRIMAL GLANDS

The lacrimal gland is a tubulo-alveolar gland of serous type. It is located in the superolateral part of the orbit, immediately behind the orbital rim within the lacrimal fossa of the frontal bone (Fig 2). It is divided into an upper (orbital) and lower (palpebral) lobe by the lateral horn of the levator aponeurosis.

Fig 2



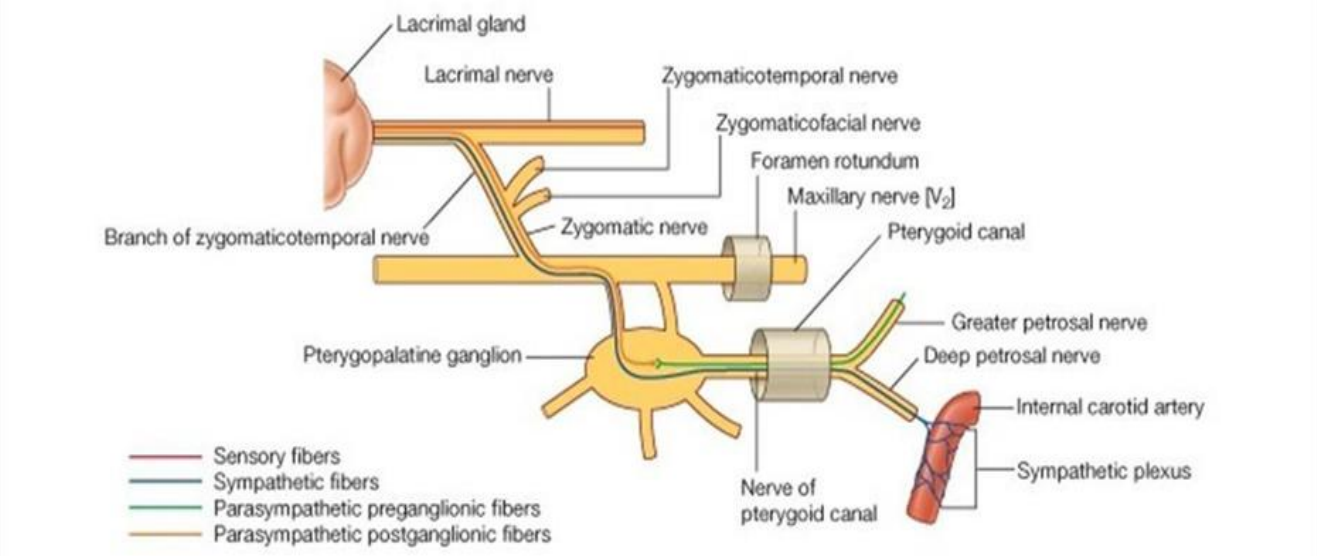
Blood Supply

- Supplied by lacrimal artery.
- Transverse facial artery also occasionally supplies the gland.
- Lacrimal veins drain the lacrimal glands and they join the ophthalmic veins[11].

Nerve Supply

- Sensory Nerve Supply is by ophthalmic nerve, first division of Trigeminal nerve (Fig 3)
- Sympathetic nerve supply is by the cervical sympathetic plexus around the carotid artery
- Parasympathetic fibres from Superior salivatory nucleus, stimulates tear secretion.[10]

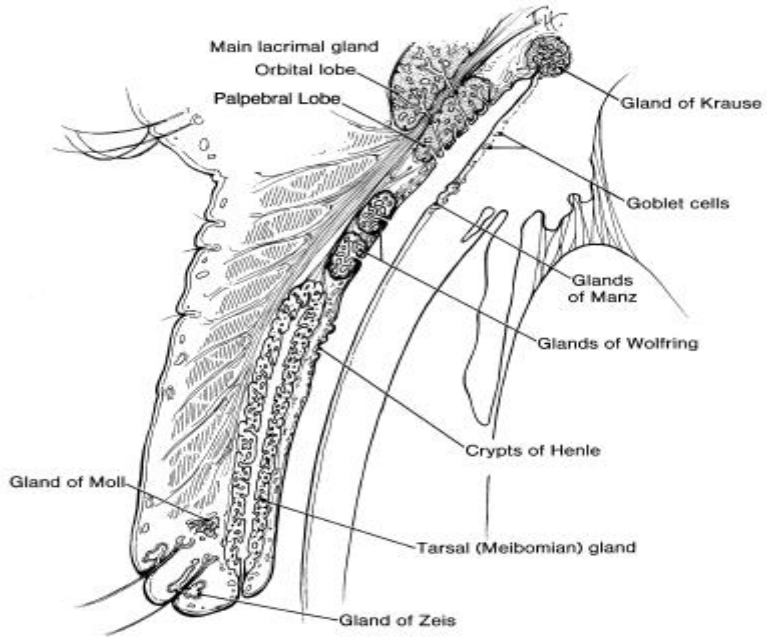
Fig 3



ACCESSORY LACRIMAL GLANDS

- **Glands of Krause:** They are situated in the palpebral conjunctiva between fornix and the edge of tarsus (Fig 4). They are more in the upper fornix than the lower fornix.
- **Glands of Wolfring:** They are located near the upper margin of the superior tarsal plate and along the inferior border of the tarsal plate of the lower lid.[11]
- **Rudimentary Accessory Lacrimal Gland:** These are present in caruncle plica semilunaris and interorbital region.

Fig 4



CONJUNCTIVAL GOBLET CELLS

They are mucin-secreting glands present in the conjunctiva. They secrete in response to the parasympathetic nerve stimulation[12].

MEIBOMIAN GLANDS

They are modified sebaceous glands situated in the tarsal plates. It consists of multiple acini, which drains through a central duct. They synthesize lipids (meibum) which form the outer layer of tear film[13].

Fig 5

GLANDS OF ZEIS

These are modified sebaceous glands that are associated with lash follicles.

GLANDS OF MOLL

These are modified apocrine sweat glands which open either into a lash follicle or directly onto the anterior lid margin between the lashes.[12]

LAYERS OF TEAR FILM

Tear film has three layers (Fig 6), outer lipid layer (0.1 μm thick), aqueous layer (7-10 μm thick) in the middle, and inner mucinous layer (0.2-1.0 μm thick).[14, 15]

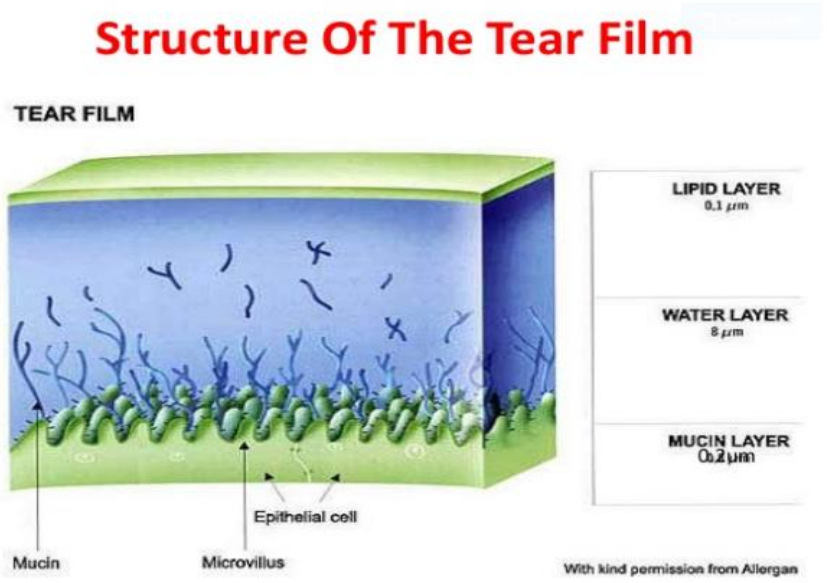
1. Mucin Layer

Microplicae and microvilli present in superficial epithelial cells of cornea and conjunctiva are essential for the even distribution of this mucin layer. This layer is secreted by goblet cells of the conjunctiva (Fig 7). It helps to lubricate the ocular surface and to trap and eliminate foreign matter. It stabilizes the tear film.

2. Aqueous layer

Main and accessory lacrimal glands contribute to the aqueous layer. It constitutes the main bulk of tear film. Aqueous layer supplies oxygen to the corneal epithelium and clears the debris and irritants and it also contains anti bacterial sub-lysozyme & betalysin.

Fig 6

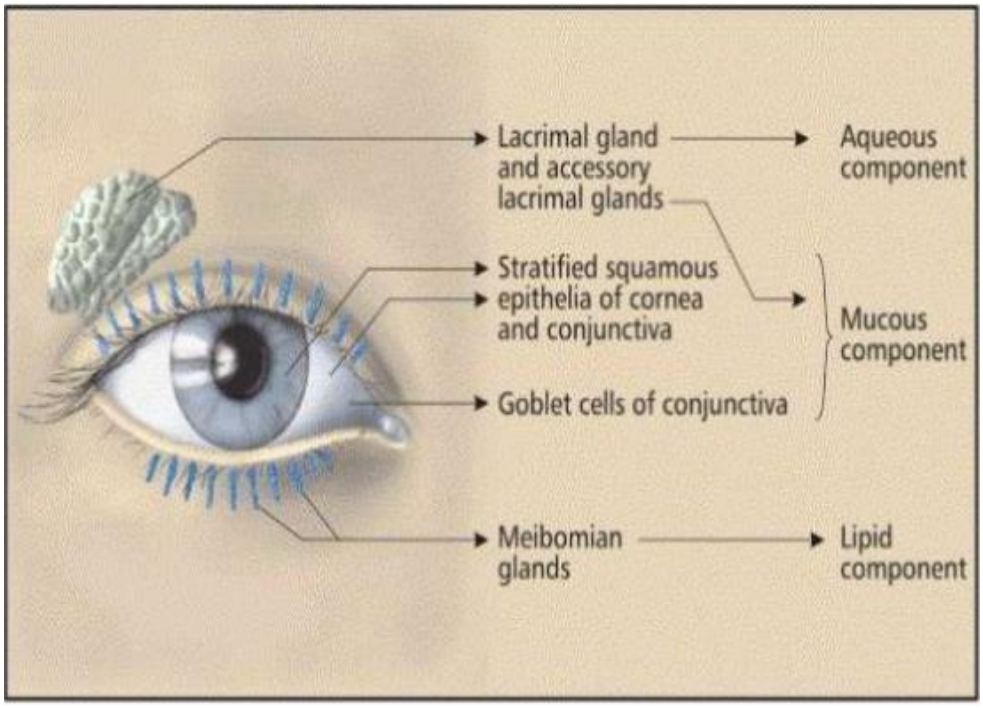


3. Lipid layer

Outermost superficial lipid layer is derived from the secretions of Meibomian, Zeis and Moll glands. It measures only 0.1 μm.[16] It prevents evaporation of the tear film.[17] It helps in preventing tear spillage from the

ocular surface. It also prevents eyelid skin damage by tears, and forms a protective seal over the ocular surface during sleep.[18]

Fig 7



COMPONENTS IDENTIFIED IN THE TEAR FILM

- Water content
- Proteins like albumin, immunoglobulin, lactoferrin, alpha-1anti trypsin and beta 2 microglobulins, mucopolysaccharides, glycoprotein, amino acids, alpha-1 anti chymotrypsin.

- Enzymes are lysozyme, glycolytic enzyme, lactate dehydrogenase, beta lysine
- Metabolites are glucose, lactate, pyruvate, urea
- Electrolytes - potassium, calcium[11]

EPIDEMIOLOGY

Dry eye is more prevalent amongst the elderly, particularly postmenopausal females.[19]

Major Epidemiologic Studies of Dry-Eye Disorders in the USA

Nurses Health Study (Schaumberg et al) shows prevalence of 5.7% less than 50years and 9.8% in more than 75 yrs old whereas Salisbury Maryland Study shows prevalence of 14.6% and similarly Beaver Dam eye study shows 14.4% prevalence.[20, 21]

DE in India:

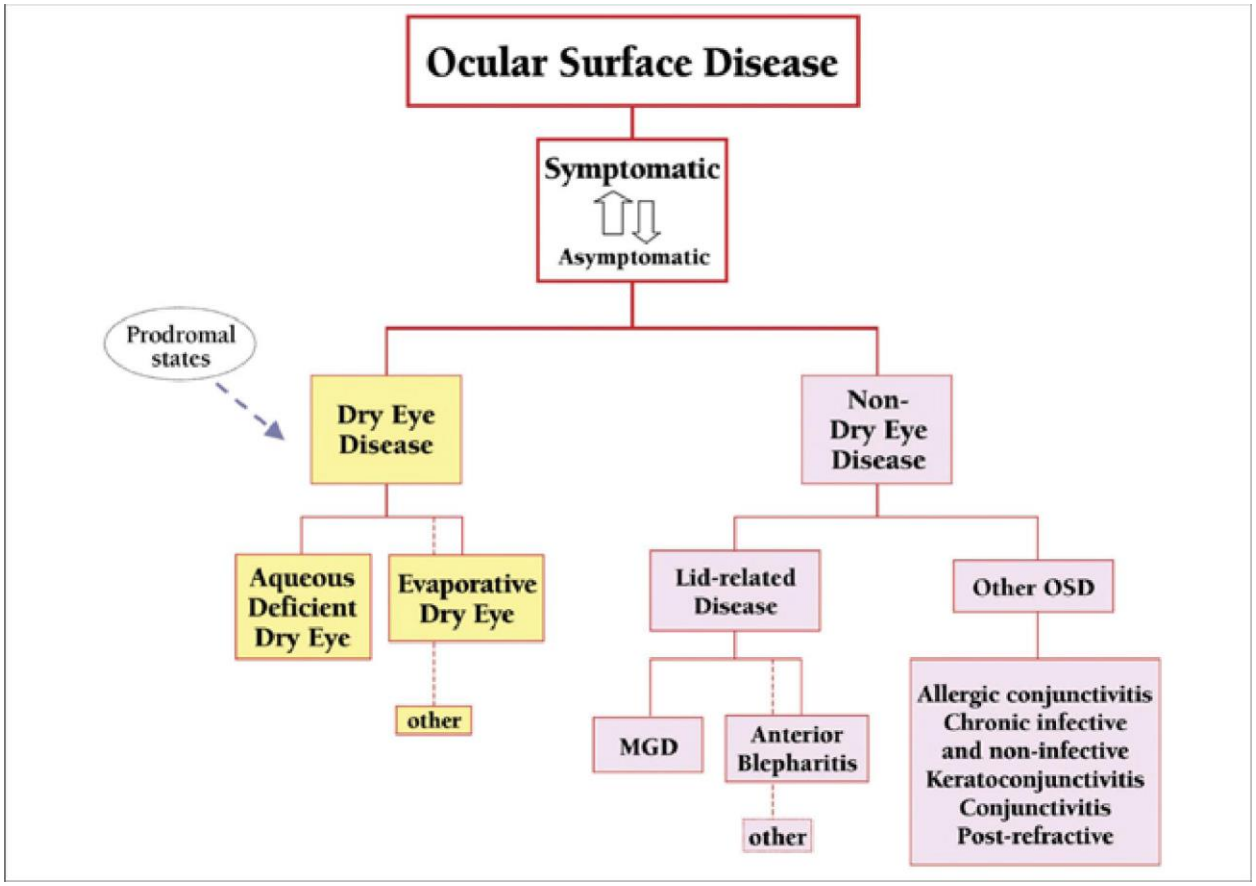
There are no published reports on the prevalence of DE in South India. In North and East Indian population the prevalence of 18.4% to 40.8% in hospital based population.[22, 23]A higher prevalence of 54% in high altitude population is noted in a study.[24]

OCULAR SURFACE DISORDERS

Ocular surface disorders include conditions causing defective production, altered composition, or distribution of tear film which may result in damage to the ocular surface.[19]

Ocular surface disorders can be classified into Dry eye disease and Non dry eye disease[25].

Fig 8



DRY EYE

Dry eye syndrome (DES) is multifactorial disease of the tears and ocular surface, which results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

Dry eye disease is further sub classified into

1. Aqueous Deficient Dry Eye (ADDE)
2. Evaporative Dry eye (EDE)

1. Aqueous deficient dry eye,

It is due to a failure of secretion of lacrimal tears. It is divided into two sub categories viz, Sjögren's Syndrome Dry Eye and non-Sjögren's Syndrome Dry Eye.

a. Sjögren's syndrome Dry Eye (SSDE)

It is the auto immune disease of the exocrine glands, in which the lacrimal and salivary glands, and other organs, are targeted by an autoimmune disease[25].

Primary Sjögren's Syndrome occurs in the absence of other discrete autoimmune diseases.[20] Secondary Sjögren's Syndrome occurs with an overt autoimmune connective disease, most commonly rheumatoid arthritis.

It presents with dry eyes, dry mouth, and evidence of an autoimmune disease.

Objective findings necessary for the diagnosis of ocular features of Sjögren's syndrome are,

- Absence of nasal-lacrimal reflex tearing
- Evidence of dry eye disorder and decreased tear break up time by ocular surface dye staining
- Serological detection of auto antibodies.

.**Diagnosis**

i. Serologic tests

  - antinuclear antibody (ANA),
  - Specific antibodies (ie, anti-Ro [SS-A], anti-La [SS-B]).
  - Anti Rheumatoid factor Antibody for Secondary Sjogren's syndrome

ii. Biopsy from lacrimal glands & accessory salivary glands

iii. Impression cytology of buccal mucosa[26].

b. Non Sjögren's Syndrome Dry Eye (Non SSDE)

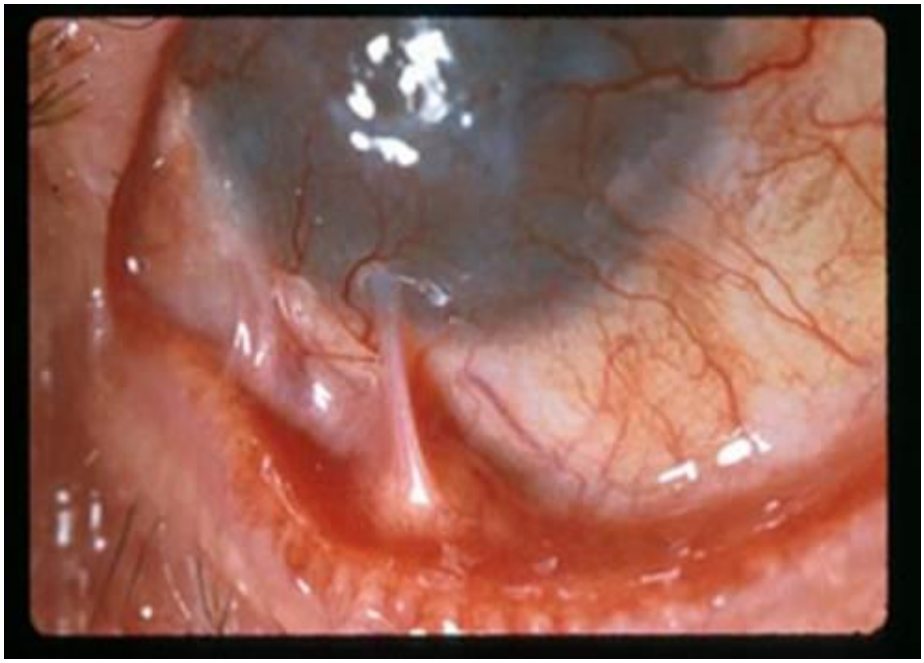
Non-SSDE is a form of aqueous deficient dry eye, where systemic autoimmune features of SSDE have been excluded[27]. Causes of Non SSDE are listed below.

1. Age related hyposecretion of lacrimal gland
2. Lacrimal tissue destruction (tumour, sarcoidosis)
3. Absence or reduction of lacrimal gland tissue.
4. Conjunctival scarring and obstruction of lacrimal gland ductules.
    i. Cicatrical pemphigoid
    ii. Stevens - Johnson syndrome
    iii. Chemical burns
    iv. Long standing trachoma
5. Reflex hypo secretion due to sensory or motor block,
6. Systemic drugs -beta-blockers, antihistamines.[12]

Steven Johnson's Syndrome

- It is mucocutaneous vesiculo bullous disease
- It is due to acute vasculitis affecting conjunctiva and other mucus membrane
- Most common drugs are Sulfa drugs (Acetazolamide), Penicillin, Barbiturate, and Salicylate.
- Membranous muco-purulent conjunctivitis leading to scarring of conjunctiva (Fig 9) and lid margin resulting in destruction of Meibomian glands, conjunctival goblet cells and limbal stem cells.

Fig 9



2. Evaporative dry eye

It is due to excessive water loss from the exposed ocular surface

Intrinsic Evaporative Dry Eye

Intrinsic evaporative eye disease is due to

- Meibomian gland dysfunction, (Meibomitis)
- Lid abnormality and poor lid dynamics
- Ocular side effects due to systemic retinoids

Extrinsic Evaporative Dry Eye

- Side effects due to toxic topical agents such as preservatives,
- Ocular surface diseases, including allergic eye disease.
- Deficiency of Vitamin A
- Contact lens wear[27]

Meibomian Keratoconjunctivitis.

- It is the most severe lid margin inflammation.
- It is mostly associated with rosacea.

- Clogging of the meibomian gland opening with desquamated epithelial cells causes inflammation.[19]

Fig 10

Meibomian gland evaluation

- By microscopic evaluation of ductal orifice, gland turbidity and viscosity.
- Meibography
- Meibometry

CLINICAL SYMPTOMS & SIGNS OF DRY EYE

- ***Mild DE:***

  - Irritation, itching,
  - Soreness, burning,
  - Foreign body sensation
  - Blurring of vision.
  - Photophobia
  - Stingy discharge

  Due to innocuous symptoms and minimal clinical signs and inconsistent correlation, milder forms are difficult to diagnose.

- ***Moderate DE:***

  There is increase in intensity of symptoms, signs and visual effects are more apparent.

- ***Severe DE:***

  There is further increase in symptoms and visual disturbances are more disabling in severe forms [28]

Table 1: DRY EYE SEVERITY GRADING[29]

Dry eye severity level	**1**	**2**	**3**	**4***
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+/++
Conjunctivalstaining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Moderate to marked	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↑↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TBUT (sec)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 min)	Variable	≤10	≤5	≤2

* Must have signs AND symptoms.

Signs

- Conjunctival injection,
- Lid edema
- Decreased tear meniscus,
- Photophobia,
- Increased tear debris,
- Loss of corneal sheen found more commonly in the exposed interpalpebral fissure.
- Disordered mucin production may lead to recurrent filamentary keratitis.
- Neo vascularisation
- Keratinization uncommonly in chronic DES and in vitamin A deficiency
- Meibomian gland inspissations, glandular dropout (seen on trans illumination of the tarsus), chalazions, and eyelash debris are signs of meibomian gland disease and blepharitis.
- Sterile ulceration of the cornea in Sjögren's syndrome - can be peripheral or paracentral[29];

DIAGNOSIS OF DRY EYE DISEASES

Evaluation of a patient exhibiting dry eye symptoms includes

- detailed patient history,
- head to toe examination to look for signs of systemic diseases causing ocular surface diseases,
- visual acquity and Fundus examination of the other eye
- Slit lamp biomicroscopy of anterior segment and detailed examination of the ocular surface and adnexa.
- Diagnostic tests.

SLIT LAMP EVALUATION

Following structures need to be examined in slit lamp

- **Eyelashes examination:** may show, distichiasis, trichiasis,
- **Eyelid margin examination:**
    - Meibomian gland abnormality & characteristics of meibomian gland secretions
- **Punctal examination:**
    - Punctal patency and position

- **Tear film examination:**
    - Height of the meniscus, debris, mucus strands may be present
- **Conjunctiva:**
    - Superior and Inferior fornix and tarsal conjunctiva examination: stellate scar(healed trachoma),extensive scarring, keratinization, fornix shortening, symblepharon.
    - Bulbar conjunctiva: e.g., punctate staining with ocular surface dye staining; follicles, hyperemia; localized drying, keratinization
- **Cornea:**
    - Corneal staining with ocular surface dye staining in punctate epithelial erosions, filamentary keratopathy, epithelial defects,
    - Keratinization, pannus formation, localized dellen, thinning, infiltrates, ulceration, scarring.[28]

DIAGNOSTIC TESTS

1. Tear break-up time (TBUT) test

- Fluorescein strip moistened with saline and applied to the inferior tarsal conjunctiva.

Fig 11

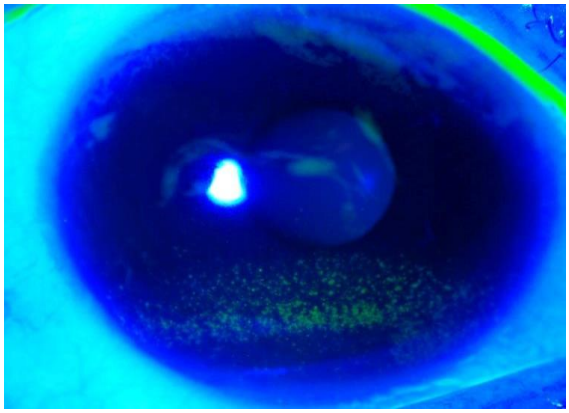
(Tear film break up viewed up with fluorescein stain on a patient with dry eye. Dry spots are indicated by the dark areas that appear on the cornea in the figure below)

- Examination of the tear film is done with slit-lamp biomicroscope with a cobalt blue filter.
- Interval between a complete blink and appearance of the first random dry spot is noted.
- Break-up time of< 10 sec is abnormal.
- A tear break-up time less than 10 sec may be seen ADDE and MGD.[30]

Ocular surface dye staining

- **Fluorescein dye test:**
  - Fluorescein strips moistened with saline is used to stain the tear film. And then the ocular surface is examined through a Slit lamp using a cobalt blue filter.
  - When there is sufficient disruption of inter cellular junctions the dye permeates into the tissue of the corneal and conjunctival epithelia.[31]
  - Five areas in cornea are examined (central, superior, inferior nasal & temporal quadrant). Each area is given a score of 0-3. Hence maximum possible score is 15.
  - Punctate or blotchy fluorescein staining is seen in dry eye and staining is more apparent on the cornea than on the conjunctiva.

Fig 12



(Fluorescein dye staining of the cornea in a patient with dry eye disease, seen through the blue filter in Fig 12)

- **1% Rose Bengal staining:**
    - Debris in tear film takes up the stain.
    - Also it stains the cells without a mucous coating .[30]
    - Red-free filter is used to examine the cornea and conjunctiva
    - As per Van Bijsterveld three quadrants; nasal conjunctiva, temporal conjunctiva and cornea are examined and each area is graded 0 – 3 according to the intensity of staining.
    - Out of total score of nine, more than four is considered abnormal.

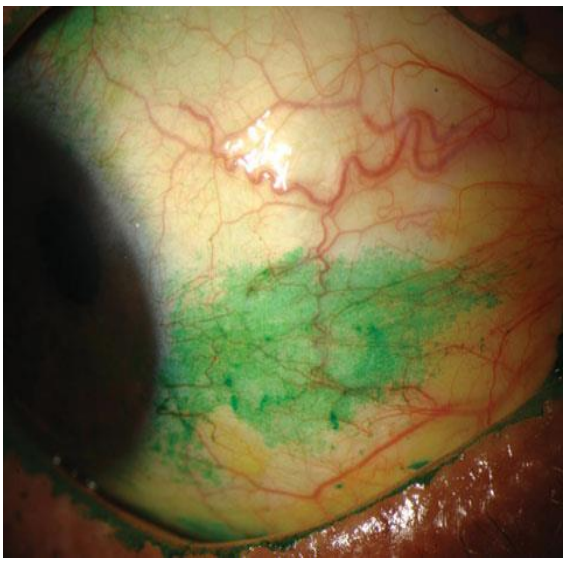
Fig 13

(Temporal and nasal conjunctiva stained by Rose Bengal stain in dry eye is shown in Fig 13)

- **Lissamine green dye:**
    - It causes less irritation than Rose Bengal stain, but staining profile is similar.[32]
    - Lissamine green detects dead or degenerated cells.

Fig 14

(Lissamine green staining the bulbar conjunctiva is shown below)



Interpretations of Ocular surface dye staining:

- Diffuse staining pattern -viral keratoconjunctivitis, medicamentosa.
- Inferior corneal & bulbar conjunctival staining -staphylococcal blepharitis, Meibomian Gland Dysfunction, lagophthalmos and exposure,

- Superior bulbar conjunctival staining -SLK.
- Interpalpebral corneal and conjunctival staining -ADDE. [33, 34]

Schirmer Test

- Aqueous tear production is assessed by Schirmer's test.
- It gives variable results.
- It is performed by placing a Whatmann Filter paper No: 41 in the lateral aspect of lower fornix.
- **Schirmer's test I**
    - Done without anesthesia
    - Assesses both basal and reflex tear secretion.
    - More than10mm of strip wetting in 5 minutes is considered normal[35]
- **Schirmer's test II**
    - Done with topical anesthesia. Adequate time should be given after the drops to minimize reflex tearing.
    - Assesses the basal secretion of tears.

Fig 15

(Schirmer's test I is shown below)

Table 2:

Characteristic Findings for Dry Eye Disease Diagnostic Testing

	Test	Characteristic findings
Aqueous tear deficiency	Tear break-up time	Less than 10 seconds considered abnormal
	Ocular surface dye staining	Pattern of exposure zone (interpalpebral) corneal and bulbar conjunctival staining - typical
	Aqueous tear production and clearance (Schirmer test)	5 mm or less for Schirmer test with anesthesia considered abnormal
Evaporative Tear Deficiency	Tear break-up time	Less than 10 seconds considered abnormal
	Ocular surface dye staining	Staining of inferior cornea and bulbar conjunctiva - typical

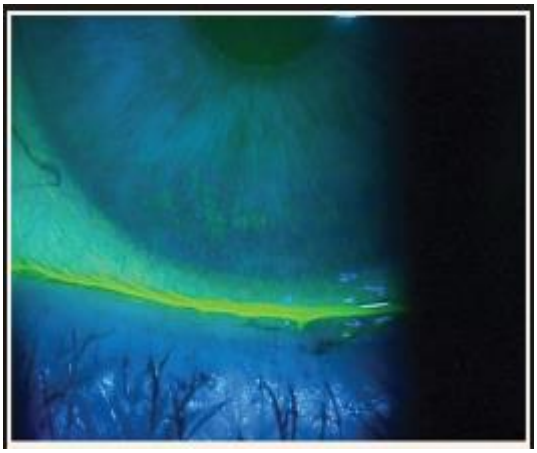
Evaluation of the tear prism.

The tear meniscus height is assessed with slit lamp examination with or without fluorescein dye.[36]

Height more than 0.2 millimeters (mm) is normal. In aqueous tear deficiency there is scanty or absent tear meniscus.

Fig 16

(Tear meniscus height seen with Slit lamp)



Tear-film debris.

Debris and particulate matter in the tear film can be visualized by biomicroscopic examination. If present it denotes inadequate flushing due to reduced tear flow.

Phenol red thread test [37]

Fig 17

- Phenol red impregnated cotton is placed in lower lateral conjunctival fornix as shown above.
- Phenol red is pH sensitive and changes from yellow to red when wetted by the tears.
- Colour change will be seen after 15 sec
- Wetting length should normally be between 9 mm to 20 mm.

Other tests done for dry eye are

- Evaluation of the pH
- Evaluation of Lysozyme &Lactoferrin content of tears

- Tear osmolarity
- Tear evaporation rate
- Conjunctival biopsy and scraping
- Impression cytology

TREATMENT

Treatment of the ocular surface disorder can be broadly divided into the treatment of primary disease causing disorder wherever applicable and treatment of ocular surface disease. Treatment of ocular surface disorder is summarized below.

WARM COMPRESSES AND LID HYGIENE

Warm compresses are indicated in patients with meibomitis or meibomian gland dysfunction. The massaging action combined with heat helps express lipid into the tear film, preventing retention of lipid within the meibomian gland.

Lid hygiene consists of cleansing the crust and scurf from the eye lashes with diluted baby shampoo[29].

TEAR SUPPLEMENTATION

Artificial tear eye substitute is most commonly prescribed to treat all kinds of ocular surface disorders. But commercially available artificial tear substitutes do not include growth factors, vitamins, and immunoglobulins which are essential for maintaining the integrity and health of ocular surface.

Artificial tear substitute often contain preservatives and additives, that are likely to elicit toxic or allergic reactions.[38]

Hypotonic and electrolyte-balanced tear substitutes are preferable, and non preserved forms are recommended if tears are to be used more than four times a day. It minimizes the chances of toxicity to surface epithelial cells due to preservatives.

AUTOLOGOUS SERUM DROPS

Recently autologous serum eye drops is routinely prescribed as an adjuvant therapy for the treatment ocular surface disorders, like dry eye disorders, neurotrophic keratitis, recurrent corneal erosion, persistent epithelial defects.[3] Human serum apart from providing lubrication, it contains substances such as EGF, vitamin A, TGF-β, fibronectin and interleukins, which are normally found in tears. They are essential for corneal &conjunctival epithelial healing and integrity.[4]

It provides essential components of tears that are reduced in ocular surface disease[5].Autologous serum, unlike artificial tear substitute does not elicit allergic reaction.

ANTI INFLAMMATORY THERAPY

Cyclosporin A

Topical cyclosporin A, a fungal-derived molecule is indicated in moderate to severe aqueous insufficiency as a result of inflammation. Topical cyclosporin decreases ocular surface inflammation and results in an improvement in Schirmer's test results and punctuates staining.

Topical Corticosteroid

Low-dose corticosteroid therapy can be used at infrequent intervals for short-term (2 weeks) suppression of discomfort and epithelial disease secondary to inflammation.

Corticosteroids if used for long term may cause cataract and steroid response glaucoma. Hence it can't be used for longer duration[29].

TETRACYCLINES

Systemic tetracyclines (Doxycycline) are useful in treating posterior blepharitis or meibomitis with or without ocular rosacea.[39]

In addition to its antibacterial properties, tetracycline inhibits collagenase activity and decreases leukocyte chemotaxis and phagocytosis.

SECRETOGOUGES

Cholinergic and muscarinic receptor agonists stimulate the secretion of mucin and tear secretion of goblet cells.

Oral pilocarpine 5-10 mg tablet twice daily is commonly prescribed.

BANDAGE SOFT CONTACT LENS

In recurrent filamentary keratopathy, soft contact lens is prescribed. But it is not prescribed in severe dry since it can exacerbate the dryness. Contact lenses should generally be avoided in neurotrophickeratopathy.[40]

OMEGA-3 FATTY ACIDS

A higher dietary intake of omega-3 an essential fatty acid, may decrease incidence of dry eye disease.[29]

SURGICAL TREATMENT

1. Punctal Occlusion

William Beetham introduced the use of punctal occlusion as a treatment for dry eye in 1935.

Punctal occlusion probably decreases tear film osmolarity by increasing the tear volume. It is useful in patients with aqueous tear deficiency, neurotrophic keratopathy and those with incomplete eyelid closure such as after blepharoplasty.

It may be

a. temporary (absorbable collagen injection and plugs - gelatin)
b. Reversible (Silicon – Acrylamide & Smart plug)
c. Permanent (Thermal & electro cautery – Laser)

2. Tarsorrhaphy

Tarsorrhaphy surgically decreases the interpalpebral surface area. It is used as a last resort in severe dry-eye disease, usually in the context of a persistent epithelial defect or corneal ulceration.

3. Other Surgical Procedures

- Amniotic membrane grafting,
- Conjunctival, limbal stem cell transplantation,
- Parotid duct and salivary gland transplantation
- Keratoprosthesis[29]

TREATMENT RECOMMENDATIONS BY SEVERITY LEVEL

Level 1:

- Stopping of causative medications
- Tear substitutes
- Anti allergic topical drops

Level II (In addition to Level I treatment)

- Preservative free tear drops and gel
- Oral and topical steroids
- Immunosuppressive topical drugs
- Secretagogues – Cholinergic receptor agonists

Level III (In addition to Level II treatment)

- Autologous serum
- Tetracyclines (Doxycycline)
- Punctal occlusion (temporary, reversible or permanent)

Level IV (In addition to Level III treatment)

- Moisture goggles to prevent evaporation of tear
- Contact lens
- Surgical procedures[29]

RECURRENT CORNEAL EROSION

Recurrent erosion of the corneal epithelium is a clinical syndrome of multiple etiologies, characterized by inadequate epithelial–stromal attachments, resulting in episodic dysadhesion and defects of the corneal epithelium.

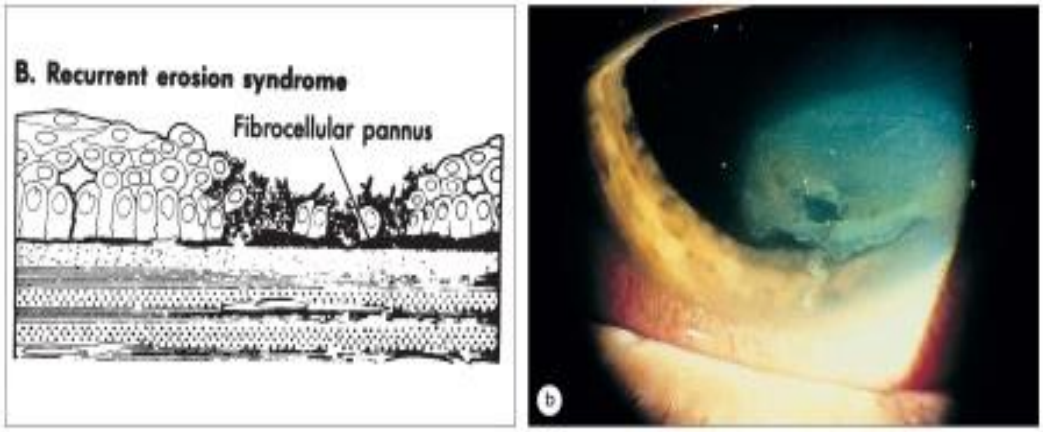
Most common etiologies are trauma and epithelial basement membrane dystrophy.

. **Pathogenesis**

Normally, the corneal epithelium is firmly anchored to the Bowman layer and stroma by specialized attachment complexes. This epithelial basement

membrane complex is responsible for tight adhesion of the corneal epithelium to the stroma. Any traumatic, dystrophic, or degenerative process of the BM can result in defective epithelial adhesion and repetitive breakdown of the epithelial cell layer.[12]

Fig 18



Diagnosis

Patients present with symptoms of

- Severe pain
- Photophobia
- Redness
- Watering present on awaking in the morning
- Prior H/O of corneal erosion
- Recurrent symptoms

Signs

- Epithelial defect in inferior interpalpebral area,
- It heals very rapidly but loosened epithelium will be seen on fluorescein examination.

Treatment

- Artificial tear drops
- Antibiotic ointment
- In severe cases bandage contact lens to alleviate the pain
- Debridement of heaped epithelium by cellulose sponge may enhance healing.
- 5% NaCl drops and ointment improves epithelial adhesions
- Following resolution lubricants can be used.
- For recurrent symptoms long term extended wear bandage contact lens
- Anterior stromal puncture reduces the recurrence rate.[15]

NEUROTROPHIC KERATITIS

It is a corneal epithelial degenerative disease due to absence of corneal sensitivity, which is characterized by impaired healing. It may result in corneal stromal melting and perforation.

Pathogenesis

In neurotrophic keratopathy there is partial or complete anaesthesia due to loss of the trigeminal innervation to the cornea.

The loss of neural influences results in intracellular oedema, exfoliation of epithelial cells, impairment of epithelial healing and loss of goblet cells, culminating in epithelial breakdown and persistent ulceration.[12]

Causes

1. Acquired damage to the 5th cranial nerve or trigeminal ganglion due to surgical ablation, stroke, aneurysm or tumour (acoustic neuroma or neurofibroma).
2. Systemic disease such as diabetes and leprosy.
3. Ocular disease such as herpes simplex and herpes zoster keratitis,
4. Abuse of topical anaesthetic,
5. Chemical burn

6. Refractive corneal surgery.
7. Congenital causes like familial dysautonomia(Riley–Day syndrome) and hereditary sensory neuropathy [15]

Fig 19

Clinical stages of neurotrophic keratitis

Stage 1

- Conjunctival staining by Rose Bengal, Punctate epithelial staining with fluorescein
- Accelerated TBUT
- Dried epithelial spots

Stage II

- Acute epithelial loss with surrounding rim of loose epithelium usually under the upper eyelid.
- Smooth and rolled out ulcer margins

Stage III

- Stromal lysis, sometimes resulting in corneal perforation

Diagnosis

1 **Corneal sensation** is tested with a wisp of cotton or an anasthesiometer (<5 mm is clinically significant).

2 **Signs**

- Interpalpebral punctate keratopathy
- Epithelial opacification, oedema and small defects.
- Persistent epithelial defect in which the epithelium at the edge of the lesion appears rolled and thickened, and is poorly attached.
- Stromal corneal melting.
- Perforation is uncommon, but occurs if there is secondary infection.

Treatment

1 Discontinuation of potentially toxic medications already in use.

2 Topical lubricant for associated dry eye or corneal exposure.

3. Autologous serum containing insulin-like growth factor-1, substance P, and neurogenic growth factor can be used

4 Protection of the ocular surface by the following:

   a Simple taping of the lids, particularly at night, for temporary protection.

   b Botulinum toxin injection to induce a protective ptosis.

   c Tarsorrhaphy may be temporary or permanent, and lateral or central, according to the underlying pathology.

   d Therapeutic silicone contact lenses

   e Amniotic membrane patch with temporary central tarsorrhaphy.[12]

PART II

AIMS AND OBJECTIVES

AIM

To compare the efficacy of autologous serum ophthalmic solution versus tear drops as adjuvant therapy in the treatment of ocular surface diseases.

PRIMARY OBJECTIVE:

To compare the efficacy of autologous serum ophthalmic solution versus tear drops as adjuvant therapy in the treatment of ocular surface diseases.

SECONDARY OBJECTIVE:

1. To document prevalence of ocular surface diseases.
2. To document the symptoms and clinical features of patients presented with ocular surface diseases

MATERIALS & METHODS:

This prospective study was conducted at Cornea services department, RIOGOH, Madras Medical College, Egmore, Chennai-08, for a period of 6 months.

Methodology:

Patient presenting with ocular surface diseases to Cornea services department, RIOGOH was registered, evaluated and followed up during the study period.

A detailed history of the patient was taken, General Examination and Slit lamp examination, and dilated fundus examination were done. Relevant Laboratory and Radiological imaging were done and recorded. Patients fulfilling the inclusion criteria were sub classified into one of the three following categories and given a serial number. Sub classifications for ocular surface diseases were (1) Severe dry eye, (2) Neurotrophic Ulcer and (3) Recurrent corneal erosion. Following parameters were recorded on presentation; fluorescein staining, Rose Bengal staining, Tear break up time, Schirmer's test. Patients will be treated as per the laid down guidelines. In addition patients with odd serial number in category will be

with autologous serum and patients with even serial number will be treated with tear drops. Symptom score and above mentioned parameters will be recorded during every follow-up. Treatment will be continued till symptoms disappear.

PREPARATION OF SERUM

Around 30 ml of blood is extracted from patient's vein without adding anticoagulant. The blood is kept in vertical position in tubes for about 2 hours to allow coagulation. Supernatant fluid is centrifuged to isolate the serum.

20% autologous serum is considered ideal because it contains certain growth factors at a concentration similar to that of natural tears[2]. Higher concentration is likely to cause irritation due to the higher viscosity. Also number of blood extraction is considerably reduced when used at lower concentration[4].

Separated serum is labeled and preserved at 4^0C. Once issued, patients are advised to preserve the serum in the refrigerator at +4°C after use[5]. Autologous serum is protected from direct sun light to prevent degradation of some of the components like Vitamin A.

SAMPLE SIZE: 30 patients

INCLUSION CRITERIA:

1. Age 15- 70 years
2. Patients with ocular surface diseases due to
    a. Severe dry eye
    b. Neurotrophic ulcer
    c. Recurrent corneal erosion

EXCLUSION CRITERIA:

1. Patients with Infectious blood borne diseases (HIV, HBV, HCV and Syphilis)
2. Patients with Anaemia and known blood dyscrasias.
3. Women who are pregnant or breast-feeding.
4. Patients unable to provide informed consent.

SCREENING PROCEDURES:

1. Detailed history of present illness,
2. Ocular symptoms on presentation
3. Signs on presentation
4. Visual acuity using Snellen's acuity chart

5. Slit lamp biomicroscopy of anterior segment
6. Fundus Examination of the same and other eye
7. Laboratory Investigations
8. Fluorescein staining, Rose Bengal staining,
9. Tear break up time,
10. Schirmer's test 1 & 2

FOLLOW UP PROCEDURES / VISITS:

Weekly in the 1st first month and twice weekly in the 2nd month.

ASSESSMENTS OF PARAMETERS:

1. Symptoms and signs on presentation and follow up.
2. Slit lamp examination
3. Tear breakup time
4. Schirmer's test
5. Rose Bengal Staining
6. Fluorescin staining

RESULTS AND ANALYSIS

Results of the patients were analyzed for statistical significance with unpaired and chi Squared test.

AGE

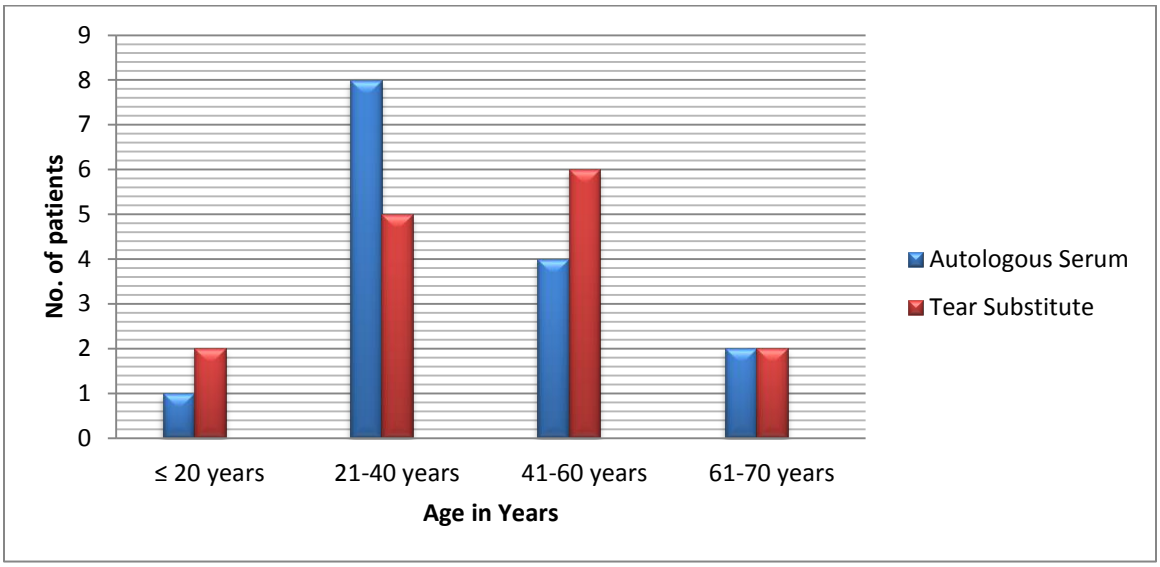
Age distribution of the patients involved in the study is depicted below.

Table 3:

Age Distribution	Autologous Serum	%	Tear Substitute	%
≤ 20 years	1	6.67	2	13.33
21-40 years	8	53.33	5	33.33
41-60 years	4	26.67	6	40.00
61-70 years	2	13.33	2	13.33
Total	15	100	15	100

Mean age of the patients is 40.5 yrs and mean age of the patients in group 1 is 39.8 yrs and group 2 is 41.87 yrs.

Fig 20



Age distribution is depicted in Bar chart (Fig 20, Tables 4 & 5)

Table 4:

Table 4 shows mean age and standard deviation in Group I and II

Age Distribution	**Autologous Serum**	**Tear Substitute**
N	15	15
Mean	39.60	41.47
SD	16.87	17.63
P value Unpaired t Test		0.7692

GENDER STATUS

There were 8 males and 7 females in Group 1 and 9 males and 6 females in Group 2 as shown in Fig 21 and Table 5.

Fig 21

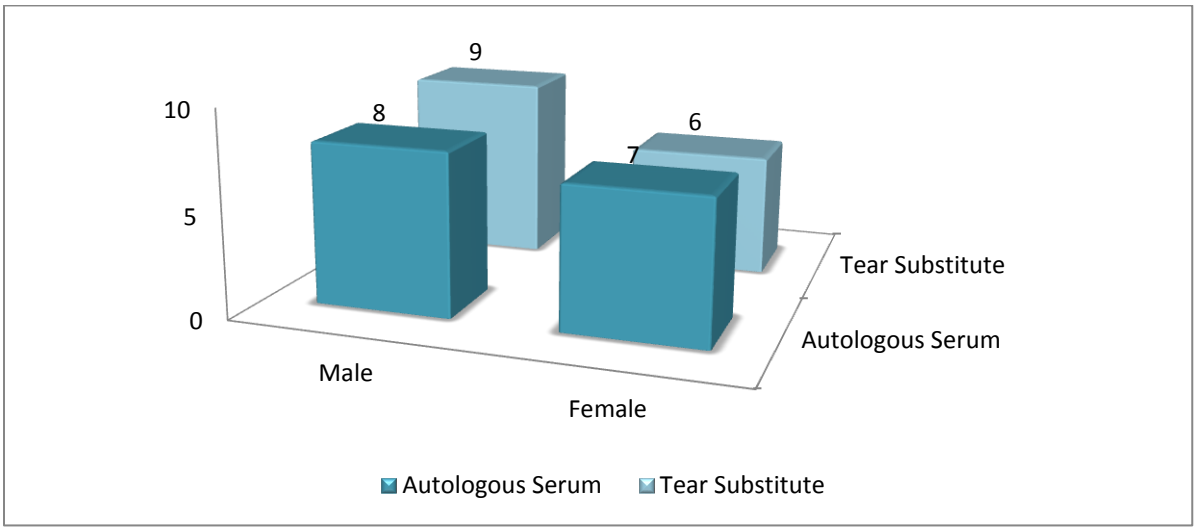


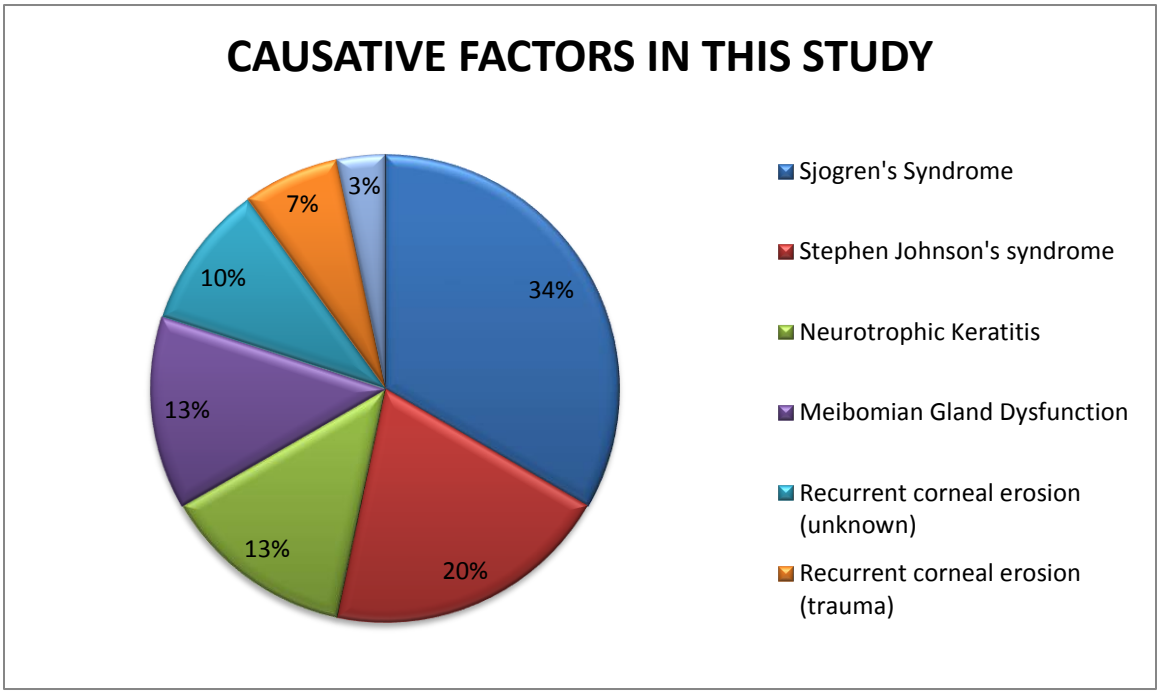
Table 5:

Gender Status	Autologous Serum	%	Tear Substitute	%
Male	8	53.33	9	60.00
Female	7	46.67	6	40.00
Total	15	100	15	100
P value Chi Squared Test		0.7126		

CAUSATIVE FACTORS IN THIS STUDY

Various causative factors for the Ocular surface disorder in this study are depicted below. Sjögren's syndrome (34%) is the most common cause in our study, followed by Steven Johnson's (20%). Neurotrophic keratitis is the causative factor for Ocular surface disorder in 13% of study population and Meibomian gland dysfunction also occurred in 13% of study population.

Fig 22



SYMPTOM SCORE

Results of each symptom score comparison is described below.

1. TEARING

Fig 23

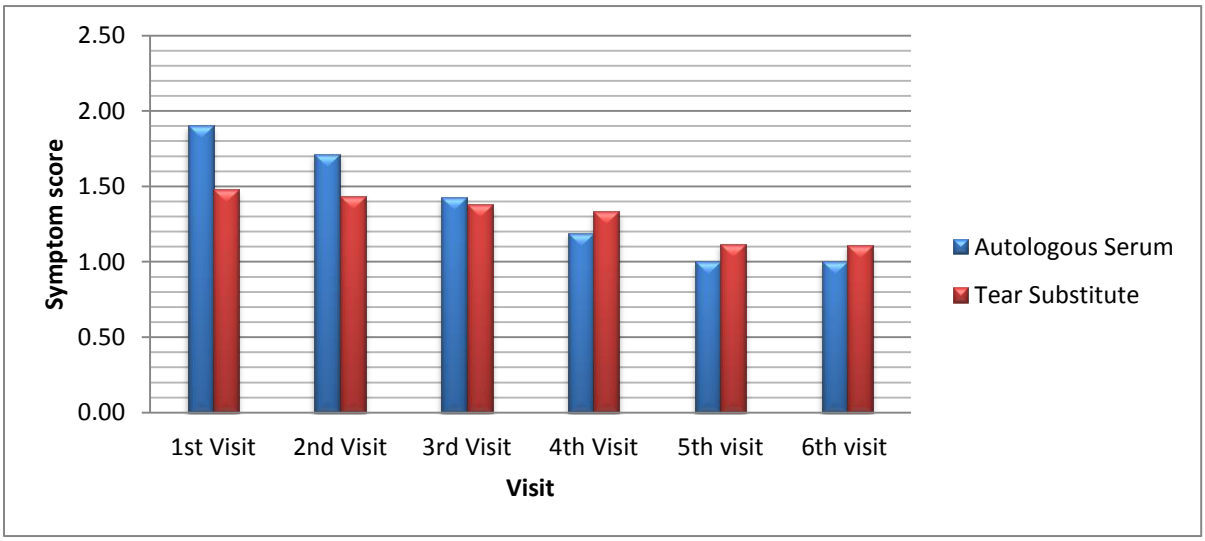


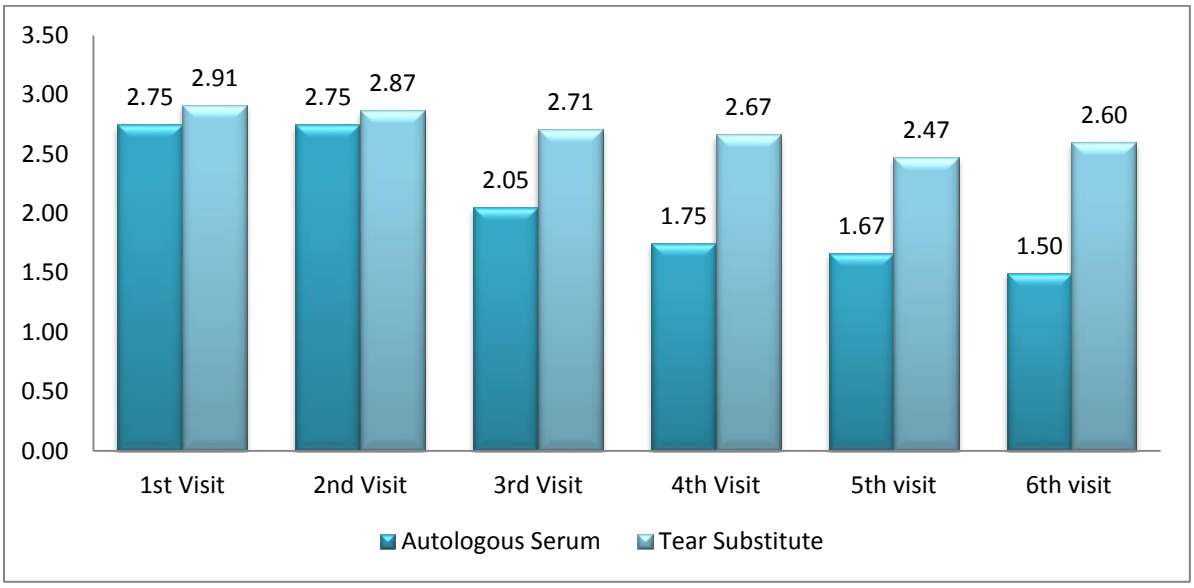
Table 6:

Tearing		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	1.90	1.71	1.43	1.19	1.00	1.00
	SD	1.00	0.85	0.51	0.40	0.00	0.00
Tear Substitute	N	23	23	21	18	17	9
	Mean	1.48	1.43	1.38	1.33	1.12	1.11
	SD	0.85	0.84	0.67	0.59	0.33	0.33
P value Unpaired t Test		0.1320	0.2790	0.7962	0.3792	0.1811	0.3051

There is no significant difference in the improvement of symptom score between autologous serum and Artificial tear substitute during the follow up period as shown above in bar chart and table.

2. BURNING

Fig 24



There was significant difference in improvement of the burning sensation of patients treated with autologous serum during 3rd, 4th and 5th and 6th visit as shown above in Fig 24 and Table 7 below.

Table 7:

Burning		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	20	20	20	20	15	10
	Mean	2.75	2.75	2.05	1.75	1.67	1.50
	SD	1.02	1.02	1.00	0.79	0.82	0.71
Tear Substitute	N	23	23	21	18	17	10
	Mean	2.91	2.87	2.71	2.67	2.47	2.60
	SD	0.85	0.92	0.90	0.84	0.80	0.70
P value Unpaired t Test		0.5701	0.6881	0.0311	0.0014	0.0086	0.0026

3. FB SENSATION

Fig 25

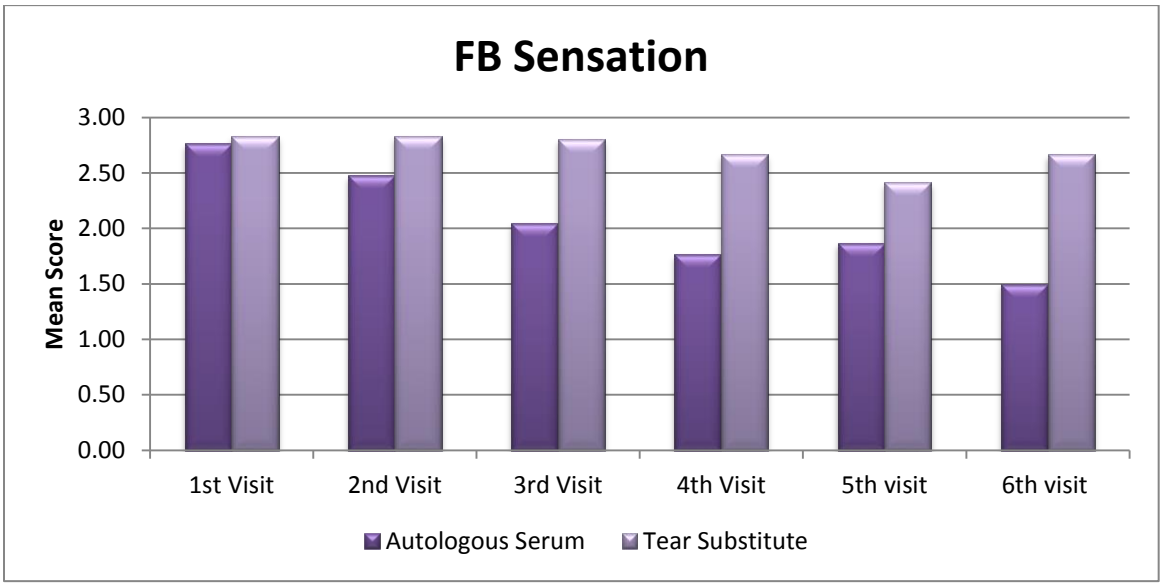


Table 8:

FB Sensation		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	2.76	2.48	2.05	1.76	1.87	1.50
	SD	0.94	0.98	0.97	0.83	0.83	0.53
Tear Substitute	N	23	23	20	18	17	9
	Mean	2.83	2.83	2.80	2.67	2.41	2.67
	SD	0.72	0.72	0.89	0.91	0.71	0.50
P value Unpaired t Test		0.7997	0.1813	0.0140	0.0025	0.0552	0.0001

There was significant difference in improvement of the foreign body sensation in patients treated with autologous serum during 3rd 4th and 6th visit.

4. PHOTOBHOBIA

There is significant difference in improvement of the photophobia of the patients treated with autologous serum during 3rd visit, 4th visit, 5th visit and 6th visit as shown in Fig 26 and Table 9 below.

Fig 26

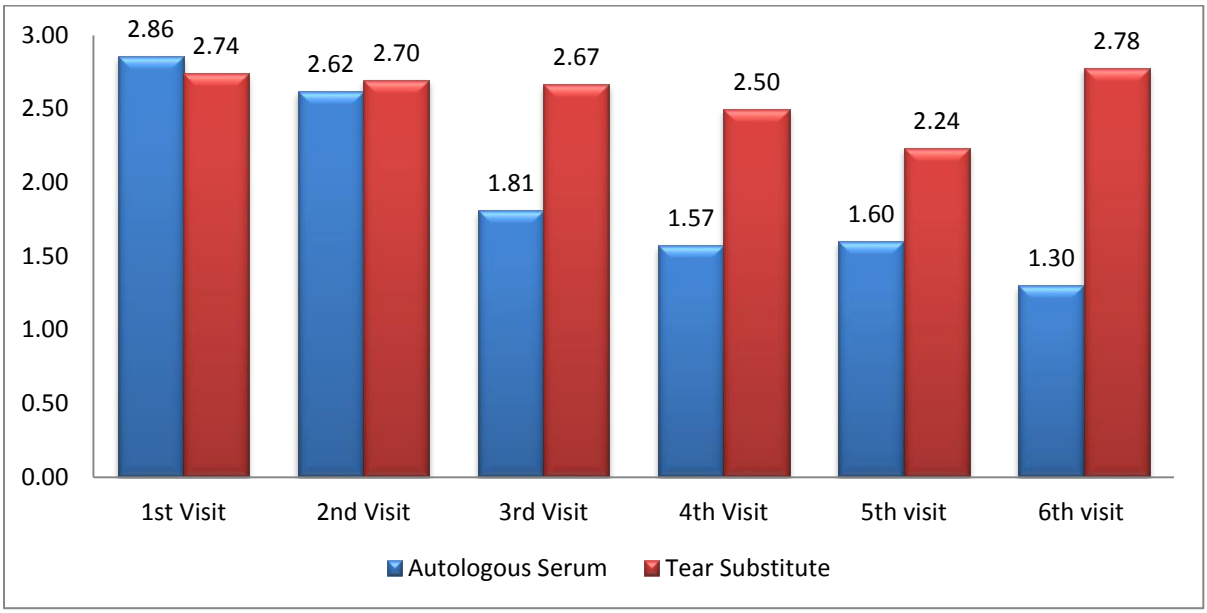


Table 9

Photophobia		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	2.86	2.62	1.81	1.57	1.60	1.30
	SD	0.85	0.97	0.98	0.75	0.83	0.67
Tear Substitute	N	23	23	21	18	17	9
	Mean	2.74	2.70	2.67	2.50	2.24	2.78
	SD	0.81	0.82	0.86	0.86	0.90	0.83
P value Unpaired t Test		0.6404	0.7787	0.0044	0.0009	0.0478	0.0005

5. BLURRED VISION

Fig 27

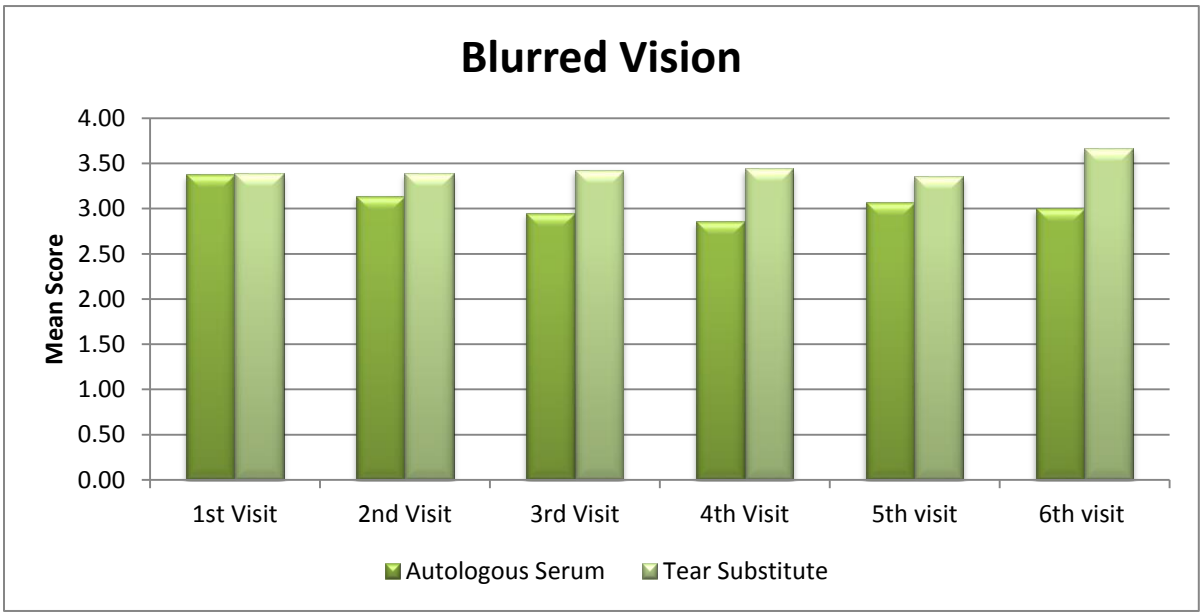


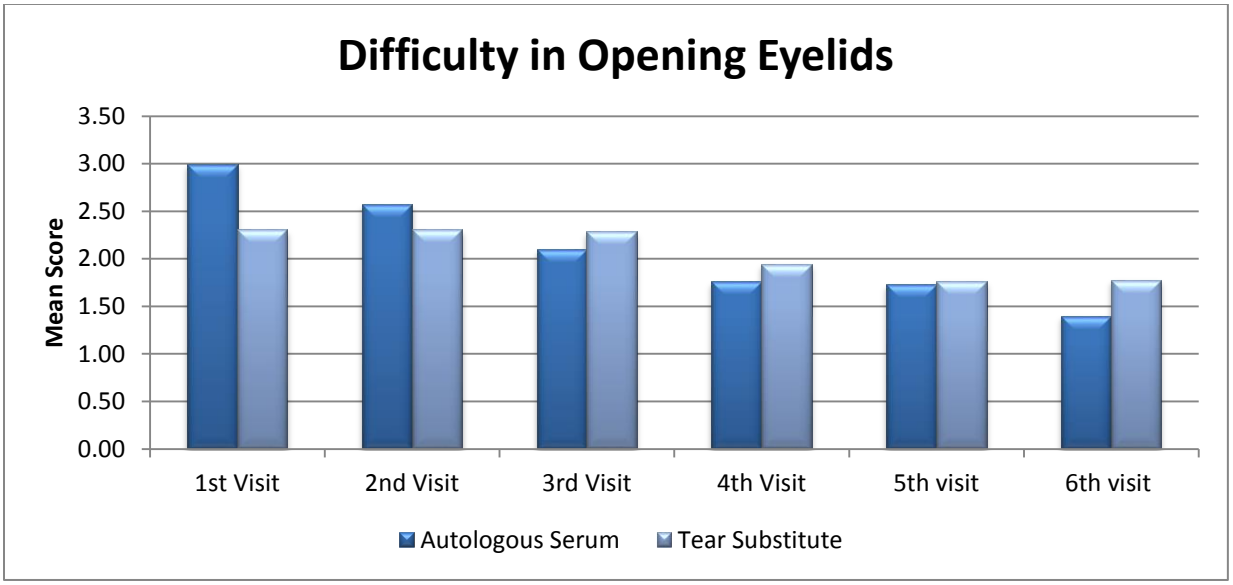
Table 10:

Blurred Vision		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	3.38	3.14	2.95	2.86	3.07	3.00
	SD	0.86	0.96	1.16	1.11	0.88	1.15
Tear Substitute	N	23	23	21	18	17	9
	Mean	3.39	3.39	3.43	3.44	3.35	3.67
	SD	0.78	0.78	0.81	0.78	0.86	0.50
P value Unpaired t Test		0.9669	0.3514	0.1311	0.0681	0.3615	0.1283

There is no significant difference in improvement in blurred vision of the patients treated with autologous serum.

6. DIFFICULTY IN OPENING EYELIDS

Fig 28



There is earlier significant improvement in difficulty in opening eyelids (1st visit) in patients treated with autologous serum as shown above (p value 0.0081).

Table 11:

Difficulty in Opening Eyelids		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	20	21	15	10
	Mean	3.00	2.57	2.10	1.76	1.73	1.40
	SD	0.89	0.87	0.91	0.77	0.80	0.70
Tear Substitute	N	23	23	21	18	17	9
	Mean	2.30	2.30	2.29	1.94	1.76	1.78
	SD	0.76	0.76	0.85	0.73	0.56	0.44
P value Unpaired t Test		0.0081	0.2848	0.5026	0.4528	0.8977	0.1827

7. STINGY DISCHARGE

Fig 29

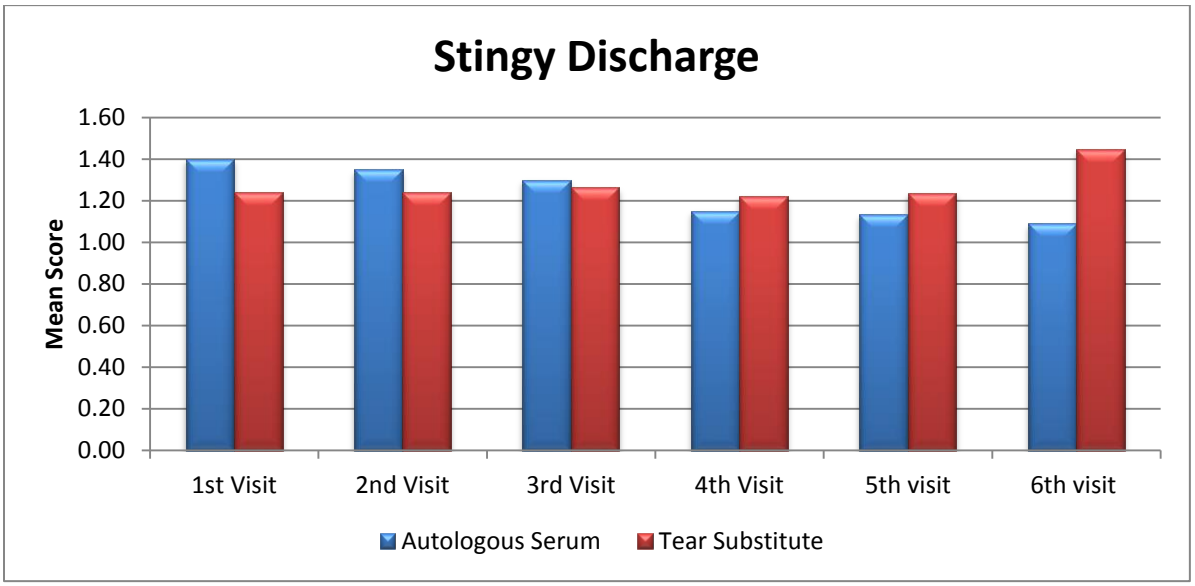


Table 12:

Stingy Discharge		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	20	20	20	20	15	11
	Mean	1.40	1.35	1.30	1.15	1.13	1.09
	SD	0.75	0.75	0.73	0.49	0.52	0.30
Tear Substitute	N	21	21	19	18	17	9
	Mean	1.24	1.24	1.26	1.22	1.24	1.44
	SD	0.70	0.70	0.73	0.55	0.56	0.73
P value Unpaired t Test		0.4802	0.6229	0.8762	0.6704	0.5989	0.1580

There is no significant difference in improvement between the patients treated with autologous serum and artificial tear substitute.

SIGN SCORES

1. LID EDEMA

There is no significant difference in improvement of lid edema in between Group 1 and 2 as shown below.

Fig 30

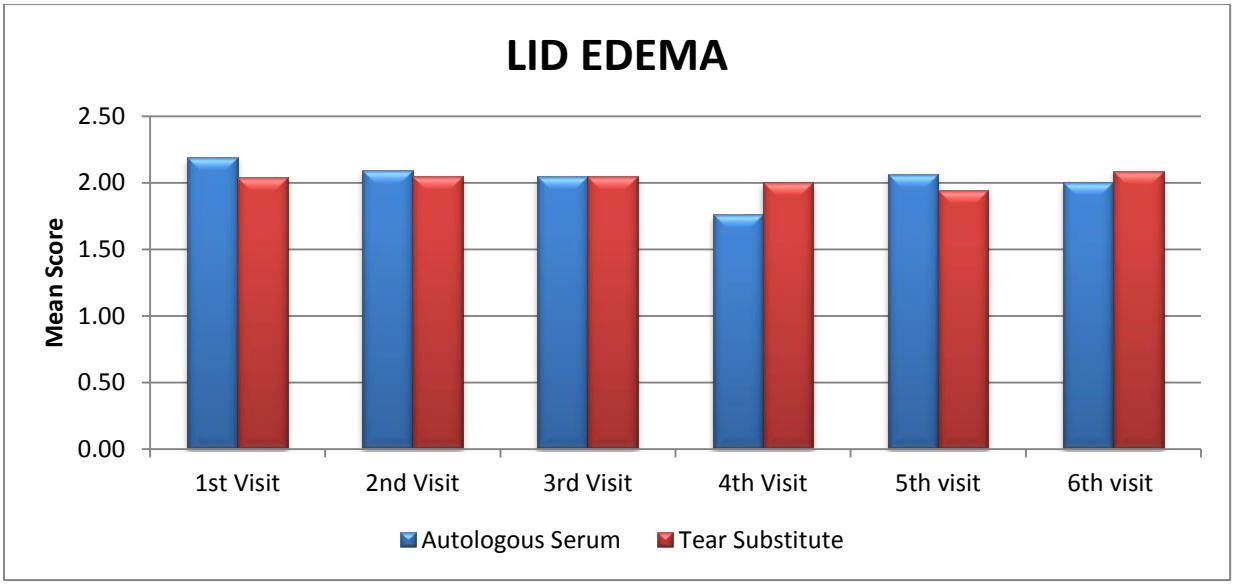


Table 13:

LID EDEMA		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	2.19	2.10	2.05	1.76	2.07	2.00
	SD	0.81	0.77	0.80	0.94	0.96	0.94
Tear Substitute	N	23	22	21	18	17	11
	Mean	2.04	2.05	2.05	2.00	1.94	2.09
	SD	0.82	0.84	0.86	0.91	0.97	0.94
P value Unpaired t Test		0.5554	0.8409	1.0000	0.4291	0.7158	0.8278

2. CONJUNCTIVAL CONGESTION

Fig 31

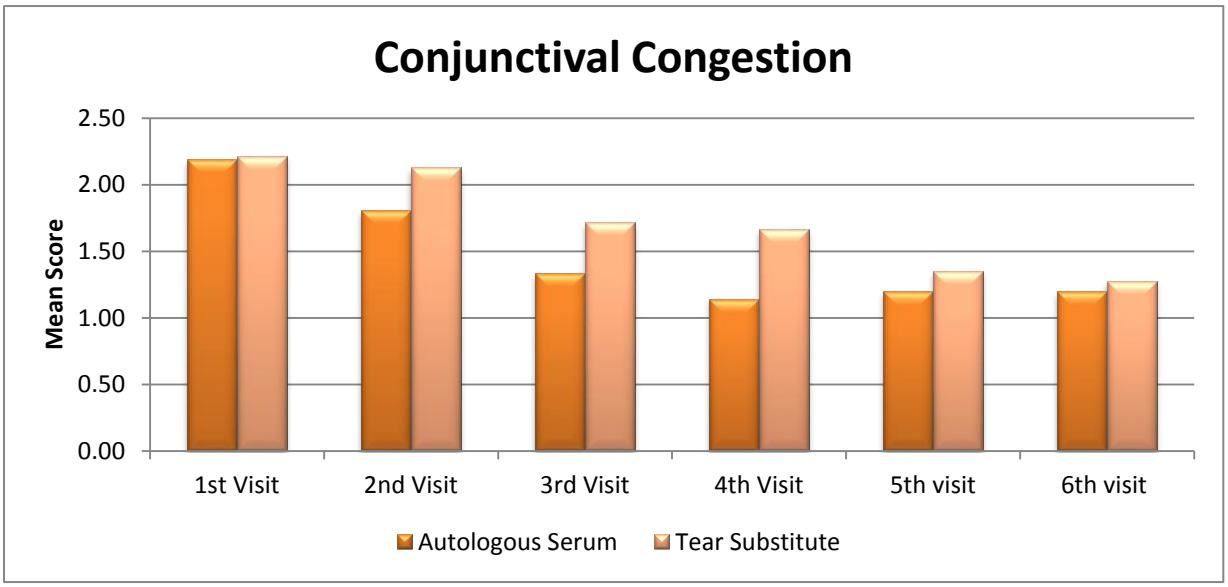


Table 14:

Conjunctival Congestion		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	2.19	1.81	1.33	1.14	1.20	1.20
	SD	0.51	0.60	0.58	0.36	0.41	0.42
Tear Substitute	N	23	23	21	18	17	11
	Mean	2.22	2.13	1.71	1.67	1.35	1.27
	SD	0.42	0.55	0.64	0.59	0.49	0.47
P value Unpaired t Test		0.8494	0.0711	0.0502	0.0017	0.3530	0.7132

There was no significant difference in improvement of conjunctival congestion during first, second and third visit but there was significant difference in improvement of conjunctival congestion during the fourth visit and there was no significant improvement in symptoms during 5th and 6th visit.

3. EPITHELIAL DEFECT

There was no significant difference in improvement of epithelial defect during 1st, 2nd, 3rd visit. There was significant difference during 4th and 5th visit as shown below

Fig 32

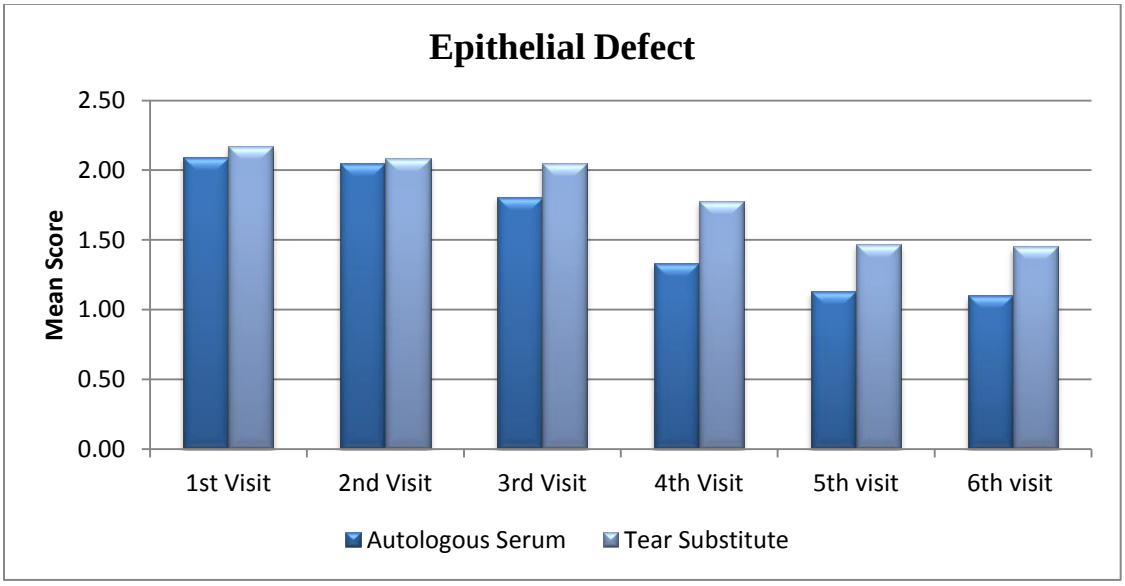


Table 15:

Epithelial Defect		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	2.10	2.05	1.81	1.33	1.13	1.10
	SD	0.62	0.59	0.68	0.48	0.35	0.32
Tear Substitute	N	23	23	21	18	17	11
	Mean	2.17	2.09	2.05	1.78	1.47	1.45
	SD	0.39	0.51	0.50	0.65	0.51	0.52
P value Unpaired t Test		0.6150	0.8144	0.2026	0.0190	0.0411	0.0789

4. NEOVASCULARISATION

There is no significant difference in improvement of neovascularisation between Groups 1 & 2 as depicted below in Fig 33 and Table 16.

Fig 33

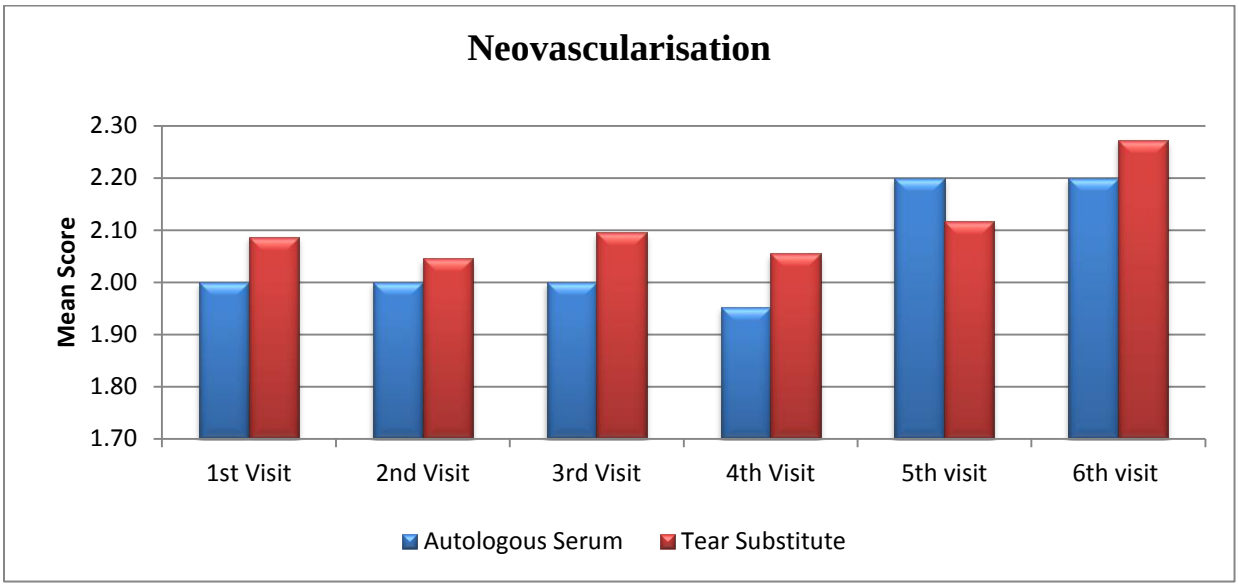


Table 16:

Neovascularisation		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	2.00	2.00	2.00	1.95	2.20	2.20
	SD	0.95	0.95	0.95	0.97	1.01	1.03
Tear Substitute	N	23	22	21	18	17	11
	Mean	2.09	2.05	2.10	2.06	2.12	2.27
	SD	0.79	0.79	0.83	0.87	0.86	0.79
P value Unpaired t Test		0.7423	0.8647	0.7311	0.7313	0.8051	0.8570

5. SCHIRMER'S TEST

Fig 34

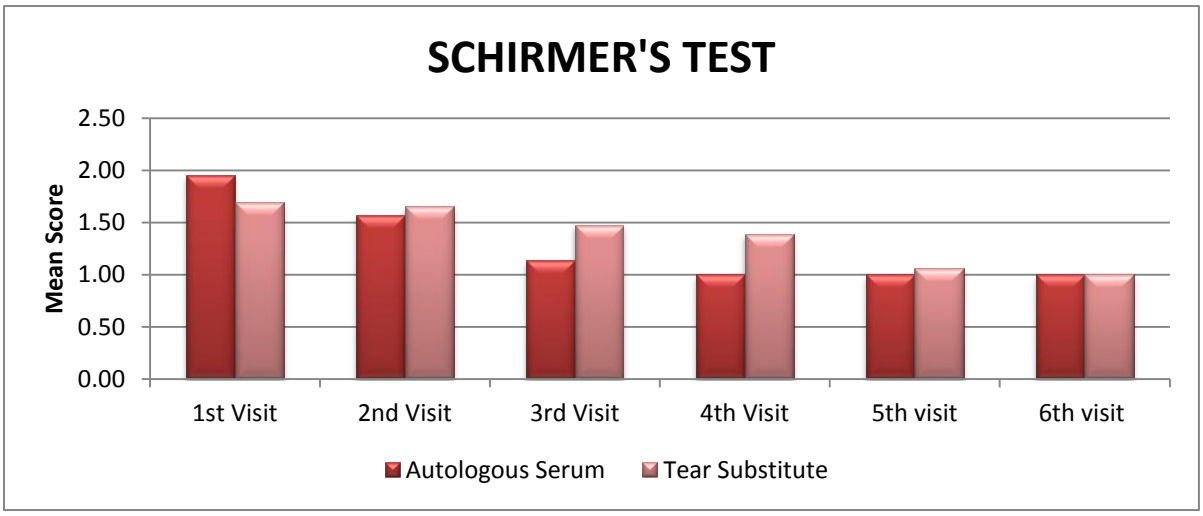


Table 17:

Schirmer's test		1st Visit	2nd Visit	3rd Visit	4th Visit	5th visit	6th visit
Autologous Serum	N	21	21	21	21	15	10
	Mean	1.95	1.57	1.14	1.00	1.00	1.00
	SD	0.38	0.51	0.36	0.00	0.00	0.00
Tear Substitute	N	23	23	21	18	17	11
	Mean	1.70	1.65	1.48	1.39	1.06	1.00
	SD	0.56	0.57	0.60	0.50	0.24	0.00
P value Unpaired t Test		0.0859	0.6245	0.0351	0.0010	0.3560	>0.9999

There is significant difference in improvement of Schirmer's paper wetting in patients treated with autologous serum during 3rd and 4th visit.

Comparison of symptoms score between Group 1 (autologous serum) with group 2 (artificial tear substitute) along with p value is tabulated below

Table 18:

Symptoms	**P value**						**Significance**
	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	
Tearing	0.1320	0.2790	0.7962	0.3792	0.1811	0.3051	No significant difference
Burning	0.5701	0.6881	0.0311	0.0014	0.0086	0.0026	Significant difference in 3rd -6th visit
FB Sensation	0.7997	0.1813	0.0140	0.0025	0.0552	0.0001	Significant difference in 3, 4th& 6th
Photophobia	0.6404	0.7787	0.0044	0.0009	0.0478	0.0005	Significant difference in 3-6th
Blurred vision	0.9669	0.3514	0.1311	0.0681	0.3615	0.1283	No significant difference
Difficulty in opening eye lids	0.0081	0.2848	0.5026	0.4528	0.8977	0.1827	Significant difference in 1st

Comparison of improvement in signs between Group 1 (autologous serum) with group 2 (artificial tear substitute) along with p value is tabulated below

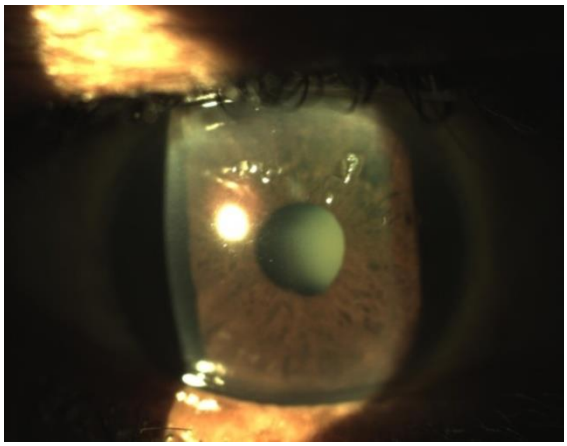
Table 19:

Signs	P value						Significance
	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	
Lid edema	0.5554	0.8409	1.0000	0.4291	0.7158	0.8278	No significant difference
Circum corneal congestion	0.8494	0.0711	0.0502	0.0017	0.3530	0.7132	Significant difference in 4th
Epithelial defect	0.6150	0.8144	0.2026	0.0190	0.0411	0.0789	Significant difference in 4th& 5th
Neovascularisation	0.7423	0.8647	0.7311	0.7313	0.8051	0.8570	No significant difference
Schirmer's 1&2	0.0859	0.6245	0.0351	0.0010	0.3560	>0.999	Significant difference in 3rd – 4th

CASE PROFILE PICTURES

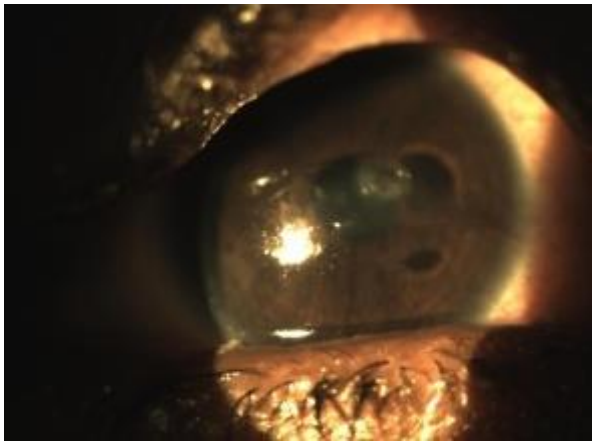
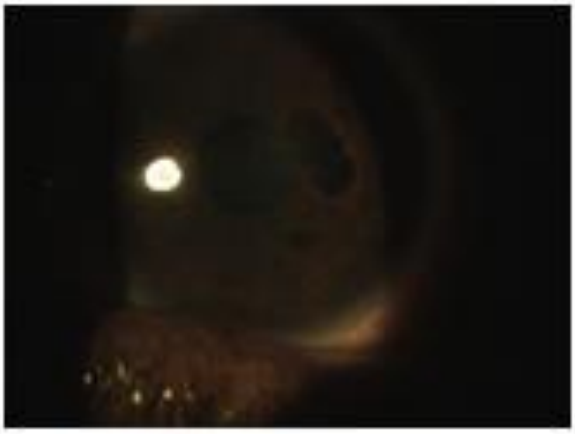
Case I: 24 yr female, a case of Sjögren's syndrome treated with autologous serum

Fig 35

Pre treatment	Post treatment
	
Epithelial defect + Schirmer's 1 & 2 < 10mm	Epithelial defect healed, in 1 month and Schirmer's 1 & 2 > 10mm

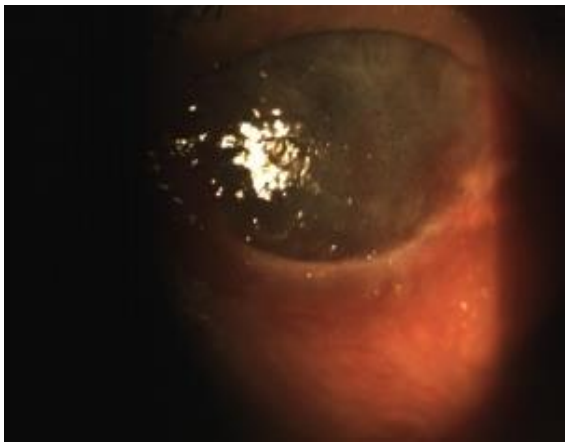
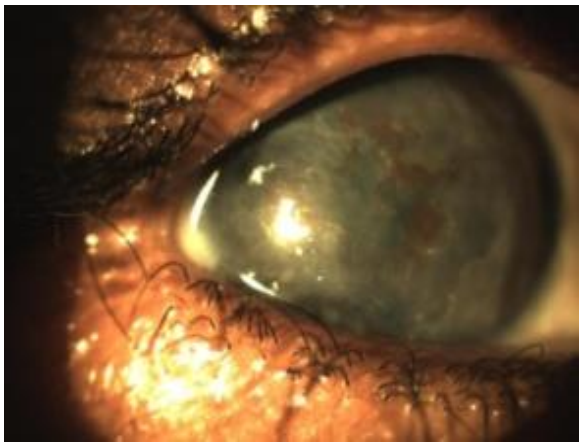
Case 2: 35 yr Female, a case of recurrent corneal erosion treated with autologous serum. Pre and post treatment pictures are shown below in Fig 36.

Fig 36:

Pre treatment	**Post treatment**
	
Epithelial defect +	Epithelial defect healed within 2 weeks

Case 3: 56 yr Female, a case of Sjögren's syndrome treated with Artificial tear substitute.

Fig 37

Pre Treatment	Post Treatment
	
Schirmer’s 1&2 < 5 mm.	Schirmer’s 1 & 2 mm < 5mm, in 1 month

DISCUSSION

AGE DISTRIBUTION

In this study 80% population in Group I (Autologous serum) and 73.33% of population in Group II (Artificial tear substitute) were between 20 to 40 yrs. Mean age of the patient is 40.5 years

Dry eye syndrome affects 10-30% of the population older than forty years in United States as per the report of Epidemiology Subcommittee of the International Dry Eye Workshop. Nurses' Health Study (Schaumberg et al) shows prevalence of 5.7% less than 50years and 9.8% in more than 75 yrs old.

In our study, the upper age limit of the patient is 70 yrs and there were stringent exclusion criteria so as to use autologous serum. Hence there is a trend towards lower age distribution in our study than in the published literature.

GENDER STATUS

Ocular surface disorder is slightly more common in women. This may be due to the fact that 90% of the patients affected with Dry Eye Syndrome due to Sjögren's syndrome are women.

In our study out of 30 patients there were 17 males and 13 females. The difference may partly be explained by different causative factors included in the

study like meibomian gland dysfunction, trauma, herpes etc. Also the women with anemia, pregnant and lactating women are excluded study which may also contribute to the discrepancy.

SYMPTOM SCORES

In our study improvement in symptom scores of the patients treated with autologous serum (Group I) is compared with the symptom score of the patients treated with Artificial tear substitute (Group II) during each visit.

In our study there is improvement in tearing, blurred vision and stingy discharge in both the groups. How ever there is no significant difference in improvement between both the groups. Finding implies that both autologous serum and artificial tear substitute are equally effective in stopping the tearing, improvement of blurring vision and stingy discharge during the follow up period.

In a study by Tanauvat et al in 12 patients treated with autologous serum there was improvement in symptoms and signs of dry eye but was not statistically significant. Similarly in our study there was no statistically significant difference in improvement of above mentioned symptoms.[40]

In this study there is significant difference in improvement of burning sensation in patients treated with autologous serum during 3^{rd} (p= 0.0311), 4^{th} (p=0.0014), 5^{th} (p=0.0086) and 6^{th} (0.0026) visit. There is significant difference in

improvement of Foreign body sensation in patients treated with autologous serum during 3rd (p=0.0140), 4th (p=0.0025) and 6th visit (p=0.0001). There is significant difference in improvement of the photophobia of the patients treated with autologous serum during 3rd visit (p=0.0044), 4th visit (p=0.0009), 5th visit (p=0.0478) and 6th visit (p=0.0005). There is also earlier significant improvement in difficulty in opening eyelids (1st visit) in patients treated with autologous serum (p value 0.0081).

Kojima et al conducted study on effectiveness of the 20% autologous serum Vs preservative free artificial tear drops for severe dry eye disease. There is significant improvement in the mean break-up time and staining scores of the patients treated with autologous serum. There was also significant improvement in subjective symptoms scores, in patients treated with autologous serum when compared with patients treated with preservative-free artificial tears.[41]

SIGN SCORES

In our study there is no significant difference in improvement of lid edema in between Group 1 and 2. There is also no significant difference in improvement of neovascularisation between the groups. In a study by Noble et al in 6 patients of Sjogren's syndrome and 5 patients of kerato conjunctivitis sicca, there was no significant improvement in Rose Bengal staining, Schirmer's test and tear clearance test.[42]

There was significant difference in improvement of epithelial defect during 4^{th} (p=0.0190) and 5^{th} visit (p=0.0411). There is significant difference in improvement of Schirmer's paper wetting in patients treated with autologous serum during 3^{rd} (p value 0.0351) and 4^{th} visit (0.0010).Tsubota et al study on effect of autologous serum on persistent epithelial corneal defect showed that the serum was effective in more than 60% of patients.[43]

Del Castillo et al studied the effect of 20% autologous serum in recurrent corneal erosions. He concluded that the autologous serum appears to be safe and effective in preventing the number of recurrences.[44]

Matsumoto et al conducted study on neurotrophic keratitis in 14 eyes of 11 patients and found that the epithelial defect healed completely in all eyes within 6 to 32 days. There was reduction in corneal scarring. Study concluded that neurotrophic factors in autologous serum may provide neurologic healers for the compromised ocular surface.

COMPLICATIONS

In our study there were no complications with the use of autologous serum and artificial tear substitute.

CONCLUSION

Autologous serum is found to be safe and significantly effective than the artificial tear substitute in the treatment of ocular surface disorders.

LIMITATIONS OF THE STUDY

- **Incidence and prevalence**

The study was not designed to bring out the incidence and prevalence of the ocular surface disorders because of the age criteria and exclusion criteria.

- **Preparation and distribution**

Preparation of autologous serum can be done in tertiary care institute with facility for withdrawing blood in adequate quality and preparation of serum. This procedure may not be feasible other set ups. Autologous serum need to be stored at 4^0C and issued in sterile container.

- **Duration of treatment**

In Chronic Inflammatory disorders like Sjögren's syndrome the serum may need to be used for a prolonged period. Hence frequent withdrawal of blood to harvest autologous serum may not be feasible.

- **Contamination**

There is risk of contamination during extraction, storage and use.

- **Recurrence of symptoms**

The study followed the patients till the continuation of treatment, so recurrence of symptoms and signs on stopping the treatment could not be commented.

PART III

ABBREVIATIONS

1.	EGF	EPIDERMAL GROWTH FACTOR
2.	TGF-B	TRANSFORMING GROWTH FACTOR-B
3.	SSDE	SJOGREN SYNDROME DRY EYE
4.	Non SSDE	NON SJOGREN'S SYNFROME DRY EYE
5.	ANA	ANTI NUCLEAR ANTIBODY
6.	SS-A	SJOGREN SYNDROME –RELATED ANTIGEN A
7.	SS-B	SJOGREN SYNDROME -RELATED ANTIGEN B
8.	DE	DRY EYE
9.	TBUT	TEAR BREAK UP TIME
10.	MGD	MEIBOMIAN GLAND DISEASE
11.	DES	DRY EYE SYNDROME
12.	ADDE	AQUEOUS DEFICIENT DRY EYE
13.	SLK	SUPERIOR LIMBIC KERATOCONJUNCTIVITIS
14.	HIV	HUMAN IUMMUNO DEFICIENCY VIRUS
15.	HBV	HEPATITIS B VIRUS
16.	HCV	HEPATITIS C VIRUS
17.	HB	HAEMOGLOBIN

18.	ESR	ERYTHROCYTE SEDIMENTATION RATE
19.	P,L,M,B,E	POLYMORPHONUCLEAR LEUKOCYTES , LYMPHOCYTES, MONOCYTES, BASOPHILS, EOSINOPHIL.
20.	VDRL	VENERAL DISEASE RESEARCH LABORATORY

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PROFORMA

Sl.No:	OP/IP No	Sub Category:	
Name:	Age:	Sex:	

SYMPTOMS

GRADE 1 TO 4

Grade 1 - no symptom
Grade 2 - Slight
Grade 3 - Moderate
Grade 4 - Severe

Symptoms	1st Visit		2nd visit		3rd visit		4th visit		5th visit		6th visit	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Tearing												
Burning												
Foreign Body Sensation												
Photophobia												
Blurred vision												
Difficulty in opening eyelids												
Stringy discharge												

SIGNS

GRADE 1 TO 3

Grade 1 - absence of signs
Grade 2 - slight
Grade 3 - severe

Signs	1st Visit		2nd visit		3rd visit		4th visit		5th visit		6th visit	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Lid edema												
Conjunctival congestion												
Slit lamp examination												
Epithelial defect Fluorescein												
Epithelial defect Rose Bengal												
Neovascularisation												
Shirmer’s test												

Laboratory Investigations

	On Presentation
Total Count	
Differential Count	P L M B E
Hb	
ESR	
HIV (Card/ELISA)	
HBV (HBsAg)	
HCV (Anti HCV)	
Syphilis (VDRL)	

Treatment Given

Drug Name	1st Visit		2nd Visit		3rd Visit		4th Visit		5th Visit		6th Visit	
Date →												
Side →												